Exhibit E

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1/TVT-O CASES**	**Master File 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF ELAINE DUNCAN, MSME, RAC

SCOPE:

I have been asked to address the developmental history, design control and risk management processes of Ethicon, Inc., Ethicon Women's Heath and Urology, a Division of Ethicon, Inc., Gynecare, and Johnson & Johnson (collectively referred to as Ethicon) associated with the design, manufacture and continuous regulatory oversight of the GYNECARE TVT Obturator (TVT-O), a medical implant device for the treatment of stress urinary incontinence for women. TVT-O represents only a design change to the delivery accessories of the original GYNECARE Tension Free Vaginal Tape (TVT).[1] The original TVT used a surgical implantation approach known as retropubic. TVT-O was designed to offer an alternative surgical implantation approach known as trans-obturator. The implanted device itself remained the same. Thus, in order to properly address TVT-O, it is necessary to include a discussion of TVT as well. My opinions are offered to a reasonable degree of professional certainty within my field of expertise and based upon my experience with medical device technology and regulation.

I have made an extensive review of documentation and testimonies, which are either specifically cited in this report or identified in Exhibit A.

BACKGROUND, EXPERIENCE, AND QUALIFICATIONS

In 1987 I founded Paladin Medical, Inc., a consulting company dedicated to the service of medical device manufacturers and developers to ensure that start-up projects and new

[1] Throughout this report, I will use the acronym "TVT" to refer to the TVT Classic product, which includes the versions of the product incorporating a needle-diameter change, a packaging change, the addition of a blue colorant, and the option of a laser cut mesh. I will use "TVT-O" to refer to the design change to the delivery system of the TVT, known as TVT Obturator.

development companies would have the benefit of an executive-level regulatory and quality assurance professional. Today the company specializes in new medical technology development and regulatory strategies.

My training in medical devices began at the University of Kentucky. I graduated from University of Kentucky in 1974 with a Bachelor of Science Degree in Mechanical Engineering, with emphasis in biomedical engineering course work and collaboration with university physicians. 3M Medical Products Division recruited me directly from UK to conduct new product development at the new surgical products division. I was immediately assigned to conduct due diligence for an acquisition of a silicone rubber implantable neurological shunt, the first acquisition of an implantable product by the company. After the comparative product assessment, I was responsible for integration of the product into the 3M quality system, designed a new sterile package for the implant, and helped the new acquisition become compliant with the nascent Good Manufacturing Practices taking effect in 1976. For nine years I was either developing patentable medical devices of my own design, or ushering in other new acquisition implants, including implantable intraocular lenses and cardiopulmonary support technology. By 1981 I had completed the coursework for a doctorate in biomedical engineering and had been awarded a Masters' Degree in Mechanical Engineering – biomedical major from the University of Minnesota, while continuing to work full-time at 3M.

In 1982, after the first human implant of the Jarvik-7 artificial heart, I set aside my academic goals when I was recruited to the start-up company evolving from the University of Utah. As the Director of Regulatory Affairs and Quality Assurance, I shepherded the new company through the FDA review prior to receiving permission for the second human case. I conducted and reported to the FDA the failure analysis of the Shiley mechanical heart valve, which caused premature removal and replacement of half of the artificial heart in the first patient only days after implant. This investigation was critical to convincing the FDA to permit the second case. I was responsible for coordinating the training curriculum program involving calf-implant surgery for the cardiovascular surgeons who would qualify for the next artificial heart implant centers. I also submitted and managed the investigational device exemption (IDE) for one of the country's first cochlear implants that was licensed to the company.

After we successfully took the artificial heart company public, I decided to return to the Twin Cities. My heart valve investigation work brought me to the attention of the "Dingell Committee," which was investigating deaths caused by failure of the Shiley Heart Valve. Although the Safe Medical Devices Act (SMDA) had passed in 1990, the Subcommittee on Oversight and Investigation of the Committee on Energy and Commerce of the House of Representatives was clearly dissatisfied by the FDA's failure to resolve the problem. I served as a consultant to the Special Assistant to the Chairman, Rep. John D. Dingell of Michigan and contributed expertise to the report entitled *FDA's Failures in Medical Device Regulation and Corporate Breach of FDA's Honor System,* published for the One Hundred 1st Congress, Second Session, February 26, 1990. Through the next few years I continued as a liaison and consultant to the Chairman's Special Assistant and the publication of the report: *Less than the Sum of its Parts: Reforms Needed in the Organization, Management, and Resources of the Food and Drug Administration's Center for Devices and Radiological Health.* By introducing committee staffers to local medical device industry leaders through the Medical Alley organization, the

committee was able to hear firsthand how improvements to regulations and practices at FDA could benefit patients and the medical device industry. Many of the reforms we recommended were implemented in subsequent regulations and guidance documents by FDA. In fact, this set off a wave of FDA and congressional delegations coming to the Twin Cities for input into the regulatory system. Regulations that were finally issued in 1996 to move from the old "good manufacturing practices" to the current Quality Systems Regulation were a direct output of that and the many interactions between the FDA and "Medical Alley" leadership.

In 1984 I was recruited to join a start-up company developing a unique, synthetic coronary artery bypass graft in collaboration with the University of Minnesota. Under my leadership of the development and quality team we established sufficient fluid mechanics performance evidence of the venturi-graft to attract support from large medical device firms and biomaterial suppliers. I planned subsequent animal and clinical trials, which led to a Humanitarian Device Exemption. When I left the company as vice-president of new ventures, the small medical device firm was well on its way with three cardiovascular product lines.

I have held a certification as a Regulatory Affairs Professional (RAC) continuously since 1994. I am a member of numerous professional associations, such as the Regulatory Affairs Professional Society, American Association of Medical Instrumentation (AAMI), and American Society of Materials Testing (ASTM)-F4 Committee. I have been an active member of LifeSciences Alley (previously-Medical Alley), including a training contributor and chair of the regulatory special interest groups.

I served for more than two decades in numerous leadership positions in the Society For Biomaterials (SFB) and continue to be involved as a contributing member to various committees. I edited and produced "***Biomaterials Forum***" for nearly a decade and sponsored workshops on Design Control and Risk Analysis Workshops. I was co-chair and chair of various specialty meetings sponsored by the Society, including a three-part series on implant retrieval and implant histology, and a symposium at the Society and World Biomaterials conventions. In addition to my service to the Society for Biomaterials, I have frequently presented to medical device training and exhibition programs around the country. I have also contributed to the trade magazine published by CANON Communications, Inc. CA. I have authored various publications in the industry press and book chapters. (See curriculum vitae for details.)

I was awarded the C. William Hall Service to the Society For Biomaterials Award in 1999 and was subsequently nominated to the Office of President. Additional recognitions include the Medical Alley Award for Outstanding Contribution to the Heath Care Industry in 1992. In 2000, I was named to the University of Kentucky Engineering Hall of Distinction and served on the Dean's Advisory Committee to the UK College of Engineering and as an advisor to the Department of Biomedical Engineering.

As the Principal of Paladin Medical, I have consulted with more than 300 client companies, including three major global medical device manufacturers, as a special projects contractor. I have provided countless hours of pro bono consulting to start-up companies, university biomedical device engineers and physicians with an idea. I have filed or supported premarket notifications [510(k)], premarket approvals [PMA], investigational device exemptions [IDE] and

Device Master Files [MAF] with the US FDA and organized Design Dossier and Technical Files for CE Mark. My clients span the globe from Austria to Australia. Through these endeavors and various professional organizations, I have provided quality assurance training to employees at numerous companies, spearheaded failure mode and effects analysis and risk assessment programs, helped to establish numerous design history files, quality manuals and quality system procedures compliant with both 21 CFR 820 Quality Systems Regulations and the comparable ISO systems (now ISO 13485:2012.); including establishment of complaint procedures and programs to support Medical Device Reporting (MDR) and Vigilance Reporting in numerous firms. I am proficient in application of ever evolving international standards to U.S. marketed devices.

I have considerable experience with software and electronic medical devices but my specialty is implantable medical devices. I have been involved with "active implantable devices," such as defibrillators and long-term biomaterial-intensive medical products, some of which integrate with human tissues and bone. For example, I have successfully applied for 510(k)s to the US FDA for surgical mesh products for companies other than Ethicon. For one such firm I worked with FDA to satisfy the needs for the FDA's 522-order for post-market surveillance. I am therefore well versed in the quality, risk assessment and validation for surgical mesh devices for various applications.

HOW MEDICAL DEVICES ARE DEVELOPED TODAY

Most ideas for a medical product derive from a physician's experience. The idea may also be born from improvements and extensions of existing technology. Typically, two or more people begin to describe product expectations, which will become design or engineering "inputs." Where there is a clear unmet need or market demand, the product emerges from the concept stage. This is not a fixed bright-line in all cases, but when commitments begin we try to establish a consensus of product description and intended use.

The feasibility stage often involves prototypes using methods and materials at hand to demonstrate that the concept can take form. Typically, more inputs are sought, a basic understanding of technology requirements evolves, and the design is further refined. Often only rudimentary testing is feasible at this time. But at the end of this stage there should be a general understanding and agreement (written) that expresses the product's intended use and an understanding of how the product fits within the marketplace. Typically at this point there is some understanding of what risks and benefits – on a general level – may be attributed to the product. A formal design review will generally capture the decision to move to development and begin to capture design development documentation.

Development stages may have several sub stages depending upon the nature of the product. For example, an implantable product might be evaluated first in an animal model and perhaps later in a clinical trial. Development stages are captured in a Design and Development Plan. The initial plan is comprehensive, but by necessity evolves and is modified as new information is gained. Although dates and resources may be mapped, the key purpose of the Design and Development Plan is to define responsibilities for implementing the plan and ensuring clear descriptions of groups and activities required for the specific development process. As an example, groups may

work on materials, sterile packaging, supporting instruments, electronics, or interface with other products. The project leader keeps these groups in focus by various key review meetings at milestone intervals or deliverables to test regimes.

Depending upon the development plan and the company's procedures, this is the time to refine "input requirements." As described above, physicians and users are major contributors to "inputs," but companies know that two additional major contributors to "inputs" cannot be ignored. First, 21 CFR Part 820 requires additional inputs to the performance and safety of medical devices. The US FDA may have also issued a guidance document on the technology or specific product which must be factored into the product design and testing plans. In fact, the guidance document may even list specific standards to which the product should adhere. Second, in some instances the FDA recognizes certain standards published by International or US standards organizations that are listed on the FDA website. Although the FDA may recognize a standard, it is not uncommon for the FDA to abridge the standard for review of premarket submissions, or refuse to recognize certain standards. See the FDA's *Guidance for Industry and FDA Staff Recognition and Use of Consensus Standards* issued on: September 17, 2007.[2] This document supersedes the "Recognition and Use of Consensus Standards; Guidance for Industry and for FDA Staff" document issued on June 20, 2001. (Note discussion below explaining that the FDA has recognized ISO 14971:2007 but has not recognized ISO 13485.)

In addition to finalization of the input requirements, hazard analysis and risk assessments at various levels (design, process, user, software, hardware – if applicable) an overall risk management scheme is refined. The risk management plan incorporates how quality assurance functions will perform through the lifecycle of the product, into production and beyond. The quality and risk management plan include the requirements for verification (usually specific physical testing against product requirements) and validation (assurance that the product meets the broader user needs, which may not always be reflected in the dimensions and physical attributes.) As with prior phases, development deliverables and reviews may be iterative. See ISO 14971:2007.

The design team analyzes the potential hazards that may occur should the product fail to meet the user (input) requirements. Thus, the team must analyze how the product may fail to achieve the requirement, and if that hazard has a potential to do harm, and the severity of the harm, should the hazard occur. And, part of the assessment is to understand how likely this potential may be. According to ISO 14971:2007, the concept of *risk* combines two variables: the probability of harm and the severity of harm. (Most failure mode and effects analysis programs also include the variable of "detectability" to help to focus on the opportunity for mitigation of the risk.)

The hazard analysis and risk assessment process is thorough and may be iterative as testing and mitigation measures affect the team's understanding of the potential to do harm and as the product moves through its various levels of evaluation. As mitigation programs take shape, the design level risk analysis is typically reviewed again to ensure that risks have been properly addressed. Sometimes risk mitigation, such as biocompatibility testing to ISO 10993, requires that the device, components, and materials are submitted to certified testing laboratories for

[2] http://www.fda.gov/RegulatoryInformation/Guidances/ucm077274.htm (last accessed February 24, 2016).

independent assays. Products are often demonstrated to expert panels and focus groups for feedback. Increasingly the ultimate validation of the performance of a new product is the conduct of clinical trials. Monitoring clinical studies and reporting results is a highly regulated process and can take many years. Throughout the clinical trial process, the regulatory body for the country in which the study is conducted has oversight of the device and clinical outcomes.

Through intensive design meetings and reviews, the team determines that outputs meet inputs and that the risks that can be mitigated are managed. Beyond design changes, mitigations can take various forms, including training of the user, labeling, and limiting the intended use. Throughout the entire project the team documents decisions and testing. Members of the team work to refine user instructions, packaging and stability data. Information the customer or user will need evolves with the understanding of the device performance.

If future design changes are required, future development teams may need to return to the development records, which (per 21 CFR 820.30j) are maintained in the Design History File. (Note: ISO 13485 does not refer to, describe, or require a Design History File, and thus "13485-based" quality systems may overlook actively compiling the necessary design history documents required by FDA.) Often design review minutes, protocols, and reports play key roles in whether or not to institute a change to a product and how to validate the change. When a change could alter an approved specification or input requirement, the team must be careful to determine how the change might affect risks, such as introducing new, unanticipated risks.

To increase efficiency of material and process validation, companies frequently refer back to materials and processes previously qualified if the analysis shows these were functional and safe. For example, TVT-O used the same Prolene mesh material as TVT. This reduces risk and improves probability estimates.

Biocompatibility is such an important part of the risk assessment process that separate ISO standards, ISO 10993, have been developed over the years to guide the need for, and means of performing, testing. For a material that has already been thoroughly tested and/or has a long history of safe clinical use in a predecessor product, little or no further testing is required. Testing usually involves sacrificing animals. Ethical standards caution against unnecessary animal testing.

Design transfer is usually viewed as the final step in the design project plan when the team agrees the product can move forward. Although design transfer to production may seem to occur at the end of the development program, in reality it has its genesis during the feasibility phase when early prototypes are crafted. Engineers must consider materials and process availability. For prototypes of small quantity manufacturing processes may be rudimentary, but as the product moves through development, the team makes prototypes which reflect the final material and methods. This is necessary so that devices qualified by way of verification and design validation truly represent the product to be marketed.

Design transfer requires that procedures and methods can ensure that the device design (that has been proven through design validation) can be manufactured. This typically translates as a final release production specification, quality control methods, and process validation. Process level failure modes and effects analysis and full process validation typify this design transfer process.

As with other stages this work may not be accomplished all at once, which is why the project participants may have additional design review meetings to ensure that all design transfer requirements are met. If a future design or material change occurs, the design transfer process may be repeated in whole or in part.

Regulatory and quality team members work hand in hand to help with the understanding of limits, standards, and FDA guidance requirements and feedback from the various project reports. Regulatory submissions and examination by standards organizations may occur at various stages throughout the development program, including during clinical trials, depending upon the nature of the product. Developmental testing could be reviewed by the FDA through an Investigation Device Exemption prior to clinical trial approval and again as part of the Pre-Market Approval process (PMA). Eventually each new product or significant change will be reviewed by the FDA. This could require a premarket notification [(510(k)], a PMA, or variations on these common agency review processes.

For devices conceived in Europe, Canada, and many Pacific-rim countries, the design development programs are similar, though some key differences still exist between FDA design control regulations and the more "ISO-based" development programs. FDA does not recognize the ISO 13485 quality system operating standard in lieu of compliance with the US federal standards for quality systems detailed in 21 CFR 820.[3] The ISO standards are not a universal medical industry standard; rather, such standards differ between countries because of different regulatory requirements. Compliance with all aspects of 21 CFR 820 is just as important today as it has ever been. FDA has never abrogated, and by law cannot abrogate, its authority for regulatory control of medical device development or manufacturing practices to any other organization, such as ISO or CEN standards. Although FDA has proposed pilot mutual recognition programs, these have only allowed a very small group of auditors based in other countries to inspect on behalf of FDA, and only if and when those same auditors have had prior successful experience in pilot-program volunteer companies.[4] Compliance with ISO 13485, in and of itself, is not sufficient to sell a product in the United States.

Medical device manufacturers strive to work with all international requirements simultaneously but in the end, each global segment may have unique requirements to be met with significant design impacts. One very typical challenge is when a device requiring electrical power must function in the U.S. with 110 volt systems but in Europe with 240 volts. Thus taking a product from one jurisdiction to another can require changes to the product already approved in a different country. Even more tedious and detailed requirements can emerge when one or more regulatory agencies adopt standard versions at different times or require modifications when adopted by their own jurisdiction. A significant example is how Canada requires its own

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm (last accessed February 24, 2016).

[4] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM212798.pdf (last accessed February 27, 2016).

modification of ISO 13485, proving the point that even standards are not really standardized.[5] Medical device design control standards must be researched for each country.

Post-market surveillance programs monitor returns, complaints, and clinical reports to ensure that the product and the user continue to perform safely for the benefit of the patient. These efforts are closely monitored by the US FDA and in most countries or jurisdictions where the devices are approved. Often mandatory reporting of any adverse event, regardless of where or when it may have occurred, is required. Some implantable medical devices are "tracked" directly to the patient and any explant of the device must be reported to FDA through a special database. Professionals in device monitoring are constantly trending reports of nonconformance, device failure, and customer complaints at any level, to determine if there is a need for product recall, design, or labeling changes. Some risks to the device are intrinsic to the technology: such as a battery in a pacemaker has a finite life. Some risks are associated with the medical intervention required to apply the device: such as anesthesia. Some risks may be a natural progression of the disease: such as coronary artery disease.

GLOBAL EVOLUTION OF MEDICAL DEVICE REGULATIONS AND STANDARDS

Despite years of attempting to harmonize global medical device standards, there still is not a single industry-quality-system standard or even a single standards organization that operates as a non-regulatory authority for medical device development. For example, ISO 13485:2003 is not the standard for design controls in Europe because the International Standards Organization developed this standard. Rather, this is the standard in Europe because the European Council (European regulatory authority) appointed CEN/CENELEC to adopt regulatory standards and then CEN/CENELEC chose to adopt this ISO as the applicable standard for design controls. In reality, this is a highly-regulated field in which regulatory authorities set standards in their particular jurisdictions. Efforts have been underway for decades to harmonize standards across international borders, without success to date.

In Sweden, the country of origin for the Ethicon TVT mesh, different parts of the European medical device directives have been transposed to a Swedish Act (SFS 1993:584), Ordinance (SFS 1993:876) and Regulations LVFS 2001:5, LVFS 2003:11 and LVFS 2001:7 by the Medical Products Agency.[6] Active implantable medical device (devices that put energy into the body) regulations were in effect from January 1, 1995. However, this effective date was not applicable to non-active mesh devices. Certification of non-active medical devices subject to LVFS 2003:11 began on 1 January 1995 but did not become mandatory until June 14, 1998. Such devices are grouped into classes (I, IIa, IIb and III), which determines the requirements for certification. With knowledge of the phase-in of these regulations from country-based to EU-based, we can understand that Medscand marketed the TVT mesh in Sweden in accordance with the rules in place at the time of the Ethicon license of the product.

---

[5] http://www.hc-sc.gc.ca/dhp-mps/md-im/qualsys/index-eng.php (last accessed February 24, 2016).

[6] http://www.google.com/url?url=http://www.s-ge.com/en/filefield-private/files/44716/field_blog_public_files/22230&rct=j&frm=1&q=&esrc=s&sa=U&ved=0CBQQFjAAahUKEwjHpfCYwPbHAhXEOpIKHT3_CCk&usg=AFQjCNH8iTZVu7zEaZ0vCiCTa2UyGEyTfQ (last accessed February 24, 2016).

In the US, The SAFE MEDICAL DEVICES ACT of 1990 amended section 520(f) of the Medical Device Law, which provided the FDA with the authority to add pre-production design controls to GMP regulations among other new requirements. FDA planned a phased implementation of the rule. It was not until October 1996 that the Federal Register issued the final rule implementing the Quality Systems Regulations to be effective June 1, 1997, and FDA allowed a one-year transition period if companies made a good faith effort to make the transition. After June 1, 1998 the FDA treated noncompliance with Design Controls the same as any other nonconformity, but for an existing device the controls became effective with a change to the device.[7]

It is important to understand the basic principle expressed in the scope of 21 CFR 820.1. It states that manufacturers need only comply with those requirements applicable to operations in which they are engaged. Thus factories or subsidiaries of a company that do not conduct certain procedures are not mandated to comply or train to those portions of the regulations. It follows that design changes made to an existing product after June 1, 1997 triggered the manufacturer to comply with Design Control and Review and have a Design History File.[8]

In Europe, the Council of European Communities has the authority to regulate medical devices. In June 1993 the Council issued Council Directive 93/42/EEC for the purpose of establishing wide-ranging new regulations designed to establish a uniform standard for quality systems for the development of medical devices in the EU.[9] But the primary purpose of Directive 93/42/EEC was to ensure that medical devices would be designed to minimize risks. The "essential objectives" of the Directive are to ensure that medical devices "provide patients, users and third parties with a high level of protection and attain the performance levels attributed to them by the manufacturers."[10] Known as the Medical Device Directive, it came into effect on 1st January, 1995; but allowed a transitional period to June 1998, within which manufacturers might choose either to apply CE Marking under the terms of the Directive or to conform to specific national regulations which allowed the product to be marketed only where such national regulations were accepted. All devices to enter the market in the EU after June 13, 1998 were required to bear CE Marking.

While the Directive sets general standards, it designated the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC) as the competent bodies to adopt more specific harmonized standards for medical device quality systems. Effective February 1997, CEN/CENELEC adopted EN 46001, to be used in conjunction with ISO 9001:1994, to define the requirements for quality systems relating to the design, development, production, installation and servicing of medical devices. (ISO 9001:1994 applies broadly to industry and EN 46001 sets the more specific requirements for medical devices.) In September 1997, CEN adopted EN 1441 as the specific standard for medical device risk analysis required by Directive 93/42/EEC. CEN later replaced EN 46001

[7] Final Rule, SMDA: Federal Register, Oct. 7, 1996, Vol 61, No 195, pgs 52602-52662.
[8] *Id.*
[9] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31993L0042. (last accessed February 24, 2016).
[10] *Id.*

when it adopted EN ISO 13485:2003. Additionally, CEN later replaced EN 1441 when it adopted ISO 14971.

The Directive established that member states (countries in the EU) would certify "Notified Bodies" to be responsible to carry out detailed examinations of manufacturers and their quality systems documentation. Thus a Notified Body must ensure that quality systems standards are met by the applicant before the CE Mark can be placed on the medical device. The certification must be renewed periodically.

This summarizes the major changes in regulations (and adoption of various operating standards) taking place in only two major arenas. During this same time many countries and regions were also adopting new rules and joining together to recognize one another's regulatory approvals. To attempt to establish some common elements and to share with other countries what had been learned, the Global Harmonization Task Force Initiative was established in 1992. Their work in certain areas also set the norms for many countries and their guidance documents are still impacting international standards on a nearly continuous basis.[11] As a global company, it is necessary for Ethicon professionals to monitor and incorporate regulations, guidance documents and standards in each of its markets into their own procedures and product expectations.

DEVELOPMENT OF TVT

Ethicon, like all medical device manufacturers, operates within a highly regulated and constantly changing industry that supports the evolving practice of medicine. Regulators in various countries reflect the expectations of their citizens and culture. Physicians reflect the expectations of a demanding clinical environment. Patients increasingly expect medical devices to solve natural biological function failures with the least inconvenience and stress. Within this context a medical device is designed to enhance benefits to the majority of patients while limiting inherent and unavoidable risks. In my opinion, Ethicon has been a leader in this endeavor with the TVT product family for urinary incontinence.

TVT is an implantable device made from PROLENE polypropylene mesh (tape). The mesh is manufactured and sold with a polyethylene sheath with a slit in the middle. Both the mesh and sheath are attached to two (2) stainless steel needles. By design, the sheath is removed with the needles during the surgical procedure, leaving only the narrow tape implant to support the urethra. The TVT Introducer (accessory) is made of stainless steel. The introducer functions to facilitate passage of the TVT device from the vagina to the abdominal skin.

It is also important to appreciate that Prolene polypropylene monofilament had been used successfully as a suture biomaterial for decades. Further, Prolene also had been used as a biomaterial for other surgical mesh applications for many years.[12] Thus, the TVT was not the first Prolene surgical mesh product. A thorough evaluation of a medical device manufacturer's compliance with industry standards for risk management requires a review of alternative methods to treat the condition for which the device is developed. There are numerous possible

[11] http://www.imdrf.org/ghtf/ghtf-archives.asp. (last accessed February 24, 2016).
[12] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K915774 (last accessed on February 24, 2016); ETH.MESH.05217103-ETH.MESH.05217144.

ways to treat SUI. There is no optimal treatment for all patients with SUI.[13] Generally, patients with SUI begin treatment with behavioral modifications. These include fluid management, timed voiding, and PFEs or Kegel exercises. Behavioral therapies result in improvement in some, but not all, SUI patients. Patients may also use absorptive devices to minimize the effect of SUI, but these devices may result in increased risk for urinary tract infections. Pharmacologic therapy has been used to treat SUI, with varying rates of success and undesirable side effects. When other options fail, surgery is an option. There are various surgical treatments for SUI, including open surgeries and laparoscopic procedures. There is also an option of using periurethral injectable agents, also referred to as bulking agents, though these therapies often must be repeated, can be allergenic, can have side effects, and results have been mixed.

In conducting any risk analysis concerning a medical device, both EN 1441:1997 and ISO 14971:2007 require consideration of the clinical history of the device or similar devices as well as consideration of input from the user community. In that regard, as previously mentioned, Prolene had been used for decades as biomaterial, both in sutures and surgical mesh.[14] Further, it is important to observe that polypropylene mesh midurethral slings ("MUS") (*i.e.*, TVT), have become the "gold standard" or "standard of care" for patients who require surgical treatment of SUI.[15] As the AUGS pointed out "there have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century."[16] A recent publication in the Nature Reviews: Urology, declared that synthetic midurethral slings "have become the gold standard first-line surgical treatment for women with uncomplicated SUI."[17]

The TVT was conceived by a physician and clinically evaluated even before Ethicon began to collaborate with Medscand. As of today, TVT has been actively monitored in the clinic for decades. As required by internal procedures for complaint trending and adverse event reporting and as required for continued CE Mark, Ethicon has specifically evaluated the performance of the TVT by physician employees and independent physician specialists. Known as Clinical Expert Reports or Clinical Evaluation Reports, it is the obligation of the company to compile, analyze and report worldwide statistics concerning complaints, adverse event reports and medical literature publications in the time since the previous CE Mark application. These CERs are an important step in the process of assuring post market that a medical device performs as expected and is safe. Such reports are thus also input to Ethicon's worldwide post-market surveillance program for TVT. Over the years, Ethicon has stayed abreast of the clinical literature and conducted periodic CERs concerning its TVT products, some of which are discussed below. The most recent 2013 CER for the TVT family of products included an

[13] Rovner, et al., Treatment Options for Stress Urinary Incontinence, *Rev. Urol.*, 2004; 6 (suppl 3):S29-S47.
[14] ETH.MESH. 09625731-ETH.MESH.09625737 (FDA's approval letter of new drug application for Prolene in 1969); ETH.MESH.06398793-ETH.MESH.06398932 (Prolene mesh).
[15] AUGS/SUFU Position Statement on Mesh Midurethral Slings (MUS) for Stress Urinary Incontinence, January 3, 2014 (ETH.MESH.14479863-ETH.MESH.14479866).
[16] *Id.*
[17] Ashley Cox, Sender Herschorn, and Livia Lee, Vol. 10, Review: Surgical management of female SUI: is there a gold standard?, Nature Reviews: Urology 78, 87 (2013).

extensive review of the clinical literature, analyzed the post market surveillance, analyzed the benefits versus risks and concluded as follows:[18]

- The literature review data, taken together with previously available clinical and preclinical data, are sufficient to demonstrate State of Art compliance with the essential requirements covering safety and performance of the GYNECARE TVT™ Family of products under normal conditions of use. No additional clinical data is required. No previously unidentified harms or hazards were identified in this review.
- No information was provided from either the literature or PMS data to indicate that any new performance issues are occurring in the clinical setting that were previously unknown.
- After manual review and analysis, no new hazards, increased risk or unexpected adverse events were noted. The clinical evidence provides support that GYNECARE TVT™ meets the Essential Requirements of the Medical Device Directive *2007/47/EC.*

It is my opinion, based upon my review of the information provided to me, that since the initiation of Ethicon's licensing of the product Ethicon has repeatedly and thoroughly examined TVT to ensure: 1) performance and 2) safety and vigilance.

1) Performance Evaluation of TVT

For medical products above a certain "risk class," a product must be examined to determine that it performs as intended. The performance of the product must be assessed in the context of the regulatory application for market entry. We cannot examine performance of a product without understanding the regulatory requirements within each jurisdiction because medical products cannot enter the market except by way of regulatory authority standards (norms).

- In the US, the performance of the product is evaluated by way of examination of the application [510(k)] through the appropriate and knowledgeable branch of the FDA. The application contents, and thus the evidence of safety and performance for a surgical mesh, follows the FDA's standard, which is "*FDA Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh*" issued March 2, 1999. This is the only recognized standard for the evaluation of surgical mesh products in the U.S.

- Ethicon's TVT 510(k) applications followed this guidance. This guidance could be referred to as an "industry norm." The US-FDA issues the guidance on its own accord instead of through the consensus process. This is a key difference from voluntary, international standards. In some instances, and in this specific instance, a "guidance document" may make reference to various organizations' publications (standards) for specific performance requirements (e.g. ISO 10993 for biocompatibility.)

- The FDA considers how well the product performs to the standards identified within the Guidance, such as sterilization testing, physical testing and shelf-life, which are

[18] ETH.MESH.10178882-ETH.MESH.10179216.

parameters guided by other national standards such as Association for the Advancement of Medical Instrumentation (AAMI) and American Society for Testing and Materials (ASTM) standards, and equivalence to a predicate. When satisfied, the FDA issues the 510(k).

- For Europe, the standards for performance for a new product receive their adjudication by way of examination of the Technical File through the appropriate and knowledgeable Notified Body (NB). The NB is a licensed surrogate for the regulatory authority. The Technical File is examined for completeness and the information contained therein about the performance of the product. The performance norms in this instance are identified as "essential requirements" which typically represent a litany of international standards and comparative analysis to alternative technologies or methods. Although an NB is not constrained by a published guidance document, most medical device notified bodies are well versed in their particular area of examination or will hire a consultant in the specialty to help advise on the suitability of the product's Technical File. When satisfied, the product is awarded a CE mark.

- In the US, when an existing product undergoes a significant change, a new 510(k) is submitted to FDA afresh and then the product is assessed to current standards. For Europe, a device is reevaluated by the Notified Body on a periodic basis to current standards in order to retain the CE mark.

I have researched the FDA's records and confirmed that Ethicon received a number of 510(k) clearances for the TVT products. These applications follow strict submission content examinations and must meet the FDA's professional, scientific review standards. It is common for such submission to include independent laboratory analysis for chemistry and biocompatibility. Physical property testing is required, often to ASTM standards requiring professionally prepared protocols and reports. If animal studies are necessary, these studies are conducted in professional laboratories following Good Laboratory Practices according to 21 CFR 58, and these studies require quality auditing during and after the study report. It is not uncommon that clinical data is also submitted with the 510(k). All clinical trials, regardless of the country in which they are conducted, must follow Good Clinical Practices, which involve trial plan approval, monitoring, and reporting during the trial. In addition, Ethicon has documentation that any change to the TVT was evaluated for whether or not the change met the FDA's criteria for a new submission.

Medscand, and then Ethicon, maintained the CE Mark for the TVT products continuously since the inception of the Directive. This demonstrates that the TVT mesh products and associated documentation were evaluated by independent, external agencies on various occasions, and in each instance the examining body determined that the product and documents met the performance standards, EN 46001 and ISO 9001 in the late 1990s and early 2000s, and ISO 13485:2003 after 2003, plus others identified in the Essential Requirements and Technical Files.

2) Safety and Vigilance:

For moderate risk medical products, the safety of the product, after the initial application for market entry, is primarily monitored through the intertwined practice of Quality Systems.

- In the US, the standards for Quality Systems are set forth in the Code of Federal Regulations 21 Part 820, sometimes called cGMPs-i.e. “current”. These standards were previously known as “Good Manufacturing Practices.” The over-arching purpose of 21 CFR Part 820, as stated in the regulation, is “to ensure that finished devices will be safe and effective.” The current regulations go beyond manufacturing to incorporate multiple levels of management oversight, design controls, self-auditing, purchasing controls, traceability and recordkeeping. These quality system standards also require post-market monitoring through complaint handling and adverse event reporting. Reports of component or product nonconformance require strict oversight and an active corrective and preventive operation. These are obligations far beyond the already strict development process requirements. The medical device manufacturer is subject to evaluation by government inspectors and auditors, not to mention required internal periodic reports to management. Companies may even hire outside auditors to help ensure unbiased appraisal of the methods which ensure oversight to the requirements. All of this nearly constant oversight is intended to ensure compliance to national and international norms that monitor product safety. Failure to meet government inspection norms can result in serious consequences for the company and suspension of the product from the market. FDA takes the most drastic steps if safety is compromised.

- To sell medical products in Europe and to hold a CE Mark, a manufacturer today must have evidence of conformance to ISO 13485:2003, but this has not always been the case. In the past the Notified Body would have examined the quality system to EN 46001, but now the technical oversight to the current standard is handled by an ISO registrar, who may or may not also be a Notified Body. These auditors examine the company’s quality system and cite recommendations for corrective actions to bring specific elements of the quality system into more perfect alignment with the standards and current practices. (The 2003 version of ISO 13485 is more closely aligned with 21 CFR 820 but FDA requirements for complaint management are more rigid, to name just one difference as an example.) If the auditor cannot confirm conformance to ISO 13485, and the company fails to make necessary corrections, the CE Mark will not be renewed.

Based on my experience, and my examination of the records, it is my opinion that Ethicon has had a long and well documented compliance history with applicable US and international standards and practices, as evidenced, by among other things, its own internal records as well as reports and certifications by independent inspectors and auditors.[19]

---

[19] ETH.MESH.14481551; ETH.MESH.07251148-ETH.MESH.07251155; ETH.MESH.06832425-ETH.MESH.06832434; ETH.MESH.14481548-ETH.MESH.14481550; ETH.MESH.14163345-ETH.MESH.14163369.

Due Diligence at License:

Ethicon's due diligence for licensing the then-existing TVT medical product from Medscand (known then as the intra-vaginal slingplasty device) was a thorough and professional undertaking.[20] During the due diligence for the licensing agreement, Design Control and Review or Quality Systems and risk analysis procedures were not yet required by US regulations, but Ethicon was already anticipating the requirements for the CE mark and the new future requirements to obtain the US 510(k). The auditing scope included the "general" USA-GMPs (referring to the Good Manufacturing Practices which had been in effect since 1976 in the US.) and ISO 9000 (current standard at the time recognized by many European regulatory authorities).[21] However, the audit also gave attention to the "new FDA Device regulations" for which the Final Rule had issued October 7, 1996; but which would not be effective until July 1, 1997. By these efforts, Ethicon demonstrated anticipation of future requirements and ensured prospective product and manufacturing requirements (not yet in effect for Medscand) could be met when they became effective. The report details corrective action Medscand would be asked to complete and mentions that other J&J resources could be brought to assistance.[22]

It is important to note that the US-GMPs of the day did not yet require a "Design History File" and design validation documentation. The EN standards in effect at the time did not require a Design History File either. Nonetheless, the team set a goal to establish the Design History File to conform to the recently issued, but not yet effective, FDA regulations within two months. Other corrective actions likewise had timely objectives, including securing the CE-mark for the product, which was not mandatory in Sweden and which was still in transition at that time. This is another example of Ethicon being proactive, rather than reactive, with respect to compliance issues as regulations continued to evolve.

Demonstrations that Ethicon promptly completed their due diligence action plan after the audits are found in (a) Medscand's commitment to meet the audit requirements[23] and (b) Ethicon's follow-up report describing Medscand's efforts to fulfill the requirements.[24] In March 1998, Ethicon and J&J corporate conducted follow up audits of Medscand to ensure that Medscand had indeed addressed the audit findings listed in the 1996 audit. This same audit also showed that Medscand's TVT system was in compliance with then current standards.[25] In order to ensure compliance with quality system standards applicable in the United States, the auditors examined to the FDA's quality system regulations (QSRs), 21 CFR Part 820. In order to ensure compliance with quality system standards applicable in the EU, the auditors correctly applied ISO 9001 and EN 46001 as the industry standards to which Medscand was required to comply. The auditors found compliance with the quality systems regulations and standards applicable at that time. The auditors reported that all issues raised in the 1996 audit had been fully satisfied. The J&J audit noted that Medscand had received the CE Mark in the interim since the previous audit and confirmed that "[A]ll GMP issues . . . were scrutinized in the audit." This means that

[20] ETH.MESH.10184398-ETH.MESH.10184408.
[21] *Id.*
[22] *Id.*
[23] ETH.MESH.10184418-ETH.MESH.10184423.
[24] ETH.MESH.01317609-ETH.MESH.01317613.
[25] *Id.*

the auditors specifically checked all of Medscand's documentation regarding TVT to make sure it complied with all requirements of 21 CFR Part 820.[26] Quality assurance professionals routinely rely upon such audit reports as satisfactory evidence of compliance with applicable industry standards.

It is my opinion, based upon my review of the records, that Ethicon met or exceeded industry best practices in their due diligence GMP/standards audit prior to the licensing agreement and properly followed through with an action plan to ensure that Medscand's TVT system would comply with the anticipated new standards.

Due Diligence when Assets Purchased

Prior to the formal development of an asset purchase team, Ethicon conducted a quality audit (March 1999) to further follow-up at the Medscand facility in accordance with the international standards ISO 9001/EN46001.[27] At the time these standards were roughly equivalent to the US FDA "general" GMPs - not inclusive of design control.

Separate and apart from Ethicon's audits, the TVT device was scrutinized multiple times by independent European auditors. In October 1997, pursuant to Directive 93/42/EEC and prior to awarding the CE Mark, Medscand had been audited by an independent Notified Body, who certified that Medscand's quality system for TVT complied with the directive.[28] The Notified Body again audited Medscand in 1998 and 1999, prior to the closing date of the asset acquisition, and reconfirmed that Medscand was in compliance with ISO 9001:1994 and EN 46001:1996.[29]

Prior to the formal asset purchase Ethicon was aware of the changes made by Medscand for the rigid catheter guide and the change to 5mm needle, which included various other customer feedback initiated changes.[30] Thus even before the asset purchase, Ethicon was monitoring customer satisfaction and clinical experience and ensuring CAPA closure. This is discussed in detail below.

When Ethicon began to contemplate the purchase of the assets of Medscand; and thus become the owner and eventually the manufacturer of TVT, the participants in the acquisition team established checklists for the process.[31] Typically this is called "due diligence" and requires extensive reviews at various levels. Two such checklist examples include one for the regulatory affairs and one for quality assurance.[32] The project of due diligence was given the name Project Tomel.

---

[26] *Id.*
[27] ETH.MESH.10185514-ETH.MESH.10185516.
[28] ETH.MESH.10586748-ETH.MESH.10586749; ETH.MESH.10588872-ETH.MESH.10588876.
[29] *Id.*
[30] ETH.MESH.10586745; ETH.MESH.01316727.
[31] ETH.MESH.09748174-ETH.MESH.09748176; ETH.MESH.09748180-ETH.MESH.09748181; ETH.MESH.10185527.
[32] *Id.*

During the asset acquisition diligence, since Ethicon was already familiar with the product (having previously filed the 510(k) application and gained US 510(k) clearance), efforts were concentrated to ensure that the proper documentation would be transferred during acquisition and to identify any deliverables required at the time of change of ownership of assets. (The 510(k) application does not require submission of the design history file to the FDA.) The CE Mark analysis by the Notified Body requires examination of the Technical File. Therefore, the QA and RA due diligence focused on these deliverables that included Design History Files and other quality documentation.[33]

Various reports in October 1999 summarized the status of the due diligence activities.[34] The regulatory team members were tasked to assess the transfer of assets (ownership) on various regulatory registrations and to confirm the translation of the Design History Files and "Technical Files" for TVT and accessories. (Technical Files are required for the CE Mark and are roughly the equivalent documents as the USFDA "Device Master Record". It should be noted that many FACTBOOKS are compiled for the purpose of these Technical File events.) Quality Assurance was tasked with setting up the test method validation program, documenting the sampling plan rationale and management of waste of raw materials. Additional activities included preparation of the transfer of manufacturing and process details (to take place subsequent to the asset purchase.) By November 1999 the due diligence team had completed their comprehensive and detailed report.[35] Manufacturing transfer was planned to occur after the acquisition of assets for various reasons, including ensuring the facilities were ready.

In March 2000, TÜ V Product Service GmBH, a Notified Body, certified that, based on its own independent audit, Ethicon's TVT complied with the quality systems requirements of ISO 9001:1994 and EN 46001:1996.[36] In July 2000, TÜV also issued to Ethicon an EC Certificate pursuant to Council Directive 93/42/EEC. Again, this certificate could not have been issued if Ethicon's design process files had not properly documented required deliverables such as design requirements, design inputs, design outputs, design verification, design validation, risk analyses and design reviews for TVT.

Based on my experience and my examination of the records, it is my opinion that:

- Ethicon was diligent in the review of documentation during the asset purchase. It was not necessary for Ethicon to develop design process documentation because it had been developed by Medscand and Medscand's compliance had been audited by Ethicon, J&J and the Danish Standards Association. Moreover, these items were included in the prior audit reports and in the due diligence reviews, as shown by the checklists and reports. Ethicon did want the files organized to ensure a Design History File could be compiled.

- Ethicon's due diligence activities included an assessment of compliance with international standards and US regulations.

[33] ETH.MESH.09748051-ETH.MESH.09748053; ETH.MESH.10185491-ETH.MESH.10185492; ETH.MESH.10185503-ETH.MESH.10185505; ETH.MESH.10185506-ETH.MESH.10185507.
[34] *Id.*
[35] ETH.MESH.10185174-ETH.MESH.10185176.
[36] ETH.MESH.10586944-ETH.MESH.10586946.

- Based upon the comprehensive checklist and reports summarizing the findings, the Ethicon QA and RA teams were thorough in their quality examination and identified actions to ensure the proper transfer of required documentation, including the information necessary for the Design History File for the TVT.

DEVELOPMENT OF TVT-O

TVT-O was designed and developed over the course of 2002-2003. The difference in the TVT-O device from the TVT device is the means by which the Prolene mesh component is implanted in the patient. TVT-O refers to the trans-obturator approach instead of the retropubic approach used for TVT.[37]

The TVT-O device is described in the IFU as: [38]

GYNECARE TVT Obturator device

The GYNECARE TVT Obturator device is a sterile, single patient use device, consisting of one piece of undyed or blue (Phtalocyanine blue, Color index Number 74160) PROLENE* polypropylene mesh (tape) approximately 1/2 x 18 inches (1.1 x 45 cm) covered by a plastic sheath overlapping in the middle. Plastic tube receptacles are attached at each end. PROLENE polypropylene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE polypropylene non-absorbable surgical suture. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. PROLENE mesh is knitted by a process that interlinks each fiber junction and that providing elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body.

GYNECARE TVT Helical Passers

The GYNECARE TVT Helical Passers are two stainless steel, curved wire passers with plastic handles that are designed to deliver the GYNECARE TVT Obturator device. Helical Passers are provided as left and right units, pre-assembled to the GYNECARE TVT Obturator device. The Helical Passer MUST not be bent or deformed in any way.

GYNECARE TVT Atraumatic Winged Guide

The GYNECARE TVT Atraumatic Winged Guide is a stainless steel accessory instrument, which facilitates the passage of the GYNECARE TVT Helical Passers through the dissection tract.

For comparison, the TVT device is described in its IFU as: [39]

[37] ETH.MESH.03932909-ETH.MESH.0393292911.
[38] ETH.MESH.00860239-ETH.MESH.00860310.
[39] ETH.MESH.05225354-ETH.MESH.05225385.

TVT DEVICE

The TVT device is a sterile single use device, consisting of one piece of undyed PROLENE* polypropylene mesh (tape) approximately 1/2 x 18 inches (1.1 x 45 cm), covered by a plastic sheath cut and overlapping in the middle, and held between two stainless steel needles bonded to the mesh and sheath with plastic collars.

PROLENE polypropylene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE* polypropylene nonabsorbable surgical suture. The mesh is approximately 0.027 inches (0.7mm) thick. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. PROLENE mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body.

TVT INTRODUCER

The TVT introducer is provided non-sterile and is reusable. The introducer is made of stainless steel. It consists of two parts, a handle and an inserted threaded metal shaft. The introducer is intended to facilitate the passage of the TVT device from the vagina to the abdominal skin. It is connected and fixed to the needle, via the threaded end of the shaft, prior to inserting the needle with the tape.

TVT RIGID CATHETER GUIDE

The TVT rigid catheter guide is a non-sterile reusable instrument intended to facilitate the identification of the urethra and the bladder neck during the surgical procedure. It is inserted into a Foley catheter **(recommended size 18 French)** positioned in the bladder via the urethra. To facilitate insertion, it can be lubricated with gel.

Thus, one can see that the TVT Prolene mesh implant is the same as the TVT-O Prolene mesh implant. The difference between the two devices is the instruments used to implant the Prolene mesh. The different surgical approach (trans-obturator versus retropubic) called for the redesigned tools. The principal reason for the development of TVT-O was to offer an alternative for those surgeons who prefer to use the trans-obturator approach rather than the retropubic approach to the surgery.[40]

Ethicon design history files and technical files for the TVT-O system are extensive, incorporate by reference appropriate segments of the TVT design history, and include very thorough records of the design controls, including risk analyses, as called for in the FDA's QSRs as well as EN 46001, EN ISO 13485, ISO 9001, EN 1441, ISO 14973:2000 and ISO 10993-1, as well as other applicable standards particular to the materials and processes.[41]

The 2003 TVT-O risk analyses explained: [42]

---

[40] ETH.MESH. 03932909-ETH.MESH.0393292911; ETH.MESH.22134268-ETH.MESH.22134269

[41] ETH.MESH.00259047-ETH.MESH.00260002 (Book 1); ETH.MESH.01317769-ETH.MESH.01318358 (Book 2); ETH.MESH.01804278-ETH.MESH.01804592 (Book 3); ETH.MESH.01318359-ETH.MESH.01318831 (Book 4); ETH.MESH.00222779-ETH.MESH.00223267 (Book 5); ETH.MESH.01318832-ETH.MESH.01319499 (Book 6); ETH.MESH.01319500-ETH.MESH.01320123 (Book 7); ETH.MESH.22134203-ETH.MESH.22134747 (2003 Technical File).

[42] ETH.MESH.00259416-ETH.MESH.00259445 (Rev. 0); ETH.MESH.02259448-ETH.MESH.02259472 (Rev. 1); ETH.MESH.02259474-ETH.MESH.02259501 (Rev. 2).

DDSA
PR602-003 / App II

Page 1 of 2

DEVICE DESIGN SAFETY ASSESSMENT (DDSA) SUMMARY REPORT
(Revision __2__)

DEVICE: (Provide a description of the overall device system)

The GYNECARE TVT Obturator is used as a surgical method to treat SUI (stress urinary incontinence) in women. The device uses new components (helical passers, winged guide, plastic tubes) to introduce the currently marketed TVT mesh implant via a trans-obturator approach. The device is a trans-obturator sub-urethral sling, which uses an inside-out ("direct") approach.

SCOPE of the DESIGN SAFETY ASSESSMENT: (Define the scope of this risk assessment)

This risk assessment was completed on (check one): ____ Device ____ Subsystem ____X__ Components

This risk assessment was performed on the new Gynecare TVT Obturator components; the helical passer, winged guide, and plastic tubes as used in conjunction with the trans-obturator placement technique. The mesh implant with its sheath covering is used in currently marketed products for the same application.

In my opinion, it was proper that the risk analyses focused on the new components that differ from the TVT device for three reasons. First, the commonly shared components had already undergone thorough risk analysis as explained elsewhere in this report. Second, the common components were already undergoing thorough post-market surveillance as explained elsewhere in this report. This surveillance was already incorporating actual field experience regarding the shared components. Field experience reinforces for a design team the customers' expectations and issues that need attention. Third, Ethicon's decision conformed to ISO 14971:2000 and its internal procedure.[43]

ISO 14971:2000 recognized that it may be appropriate to only perform new risk analysis on a system accessory:

3.6 Risk management file

For the particular medical device or accessory being considered, the results of all risk management activities shall be recorded and maintained in the risk management file.

[43] ETH.MESH.10619605-ETH.MESH.10619621; ETH.MESH.10619307-ETH.MESH.10619319.

4 Risk analysis (Steps 1, 2, and 3 of Figure 2)

4.1 Risk analysis procedure

Risk analysis, as described in 4.2 to 4.4, shall be performed, and the conduct and results of the risk analysis shall be recorded in the risk management file.

NOTE—If a risk analysis is available for a similar medical device, it may be used as a reference provided it can be demonstrated that the processes are similar or that the changes that have been made will not introduce significant differences in results. This should be based on a systematic evaluation of the changes and the ways they can influence the various hazards present.

In addition to the records required in 4.2 to 4.4, the documentation of the conduct and results of the risk analysis shall include at least the following:

a) a description and identification of the medical device or accessory that was analyzed;

b) identification of the person(s) and organization which carried out the risk analysis;

c) date of the analysis.

The more recent ISO 14971:2007, which is now recognized by the FDA as a consensus standard, continues to recognize that a risk analysis can be limited in cases where a change is being made to an existing product:

4.1 Risk analysis process

Risk analysis shall be performed for the particular medical device as described in 4.2 to 4.4. The implementation of the planned risk analysis activities and the results of the risk analysis shall be recorded in the risk management file.

NOTE 5 The scope of the risk analysis can be very broad (as for the development of a new device with which a manufacturer has little or no experience) or the scope can be limited (as for analysing the impact of a change to an existing device for which much information already exists in the manufacturer's files).

Ethicon also performed a process FMEA for the TVT-O device[44] Although a design FMEA was not needed for the TVT-O mesh component, it was appropriate for Ethicon to conduct this process FMEA for the new manufacturing processes.

In my opinion, Ethicon's design history files and technical files for the TVT-O system demonstrate that Ethicon maintained a proper quality management system, including proper means whereby clinical experience was fed directly into the focused TVT-O team. Based on the documents I reviewed, the methods used by Ethicon were in compliance with the applicable medical industry standards for design controls and risk analysis.

OTHER MODIFICATIONS and IMPROVEMENTS by ETHICON

It is my opinion, based on my review of the documents provided, that Ethicon complied with applicable industry regulations and standards in the design and development of the TVT and TVT-O products with blue mesh and laser cut alternate manufacturing method. I have examined these records and will summarize the efforts made by two design teams over two years.

[44] ETH.MESH.00259913-ETH.MESH.00259921.

Blue:

TVT mesh was initially made using only clear Ethicon Prolene monofilament, like the biomaterial Prolene sutures and as used for the Prolene hernia mesh. Particularly in the bright white light used in laparoscopy, clear mesh can reflect light. Ethicon received requests from doctors to add color to the mesh to enhance visibility.[45] Ethicon Somerville was responsible for the design change control to the mesh component, which combined clear monofilament with some blue monofilament to create a blue mesh. Ethicon already had experience with similar blue Prolene sutures. The Somerville team was responsible for the biocompatibility assessment for the blue mesh, specification for the addition of the blue fibers to the component, and verification testing to ensure that the new mesh met quality requirements. This team also defined the validation protocols to be conducted to confirm improved visibility of the blue mesh, and the proportion of blue monofilament fiber to use in making the blue mesh. This team determined that the blue mesh would require a new premarket notification to the US FDA and made that submission.[46]

Although the Somerville team qualified the new blue mesh component, Ethicon Norderstedt remained responsible for TVT product design control and review, and thus was responsible for the design validation review and design transfer to production of TVT-blue.[47]

The biocompatibility assessment concluded that given the extensive history of safe clinical use of both clear and blue Prolene, the device is “intrinsically safe and without significant adverse effects for patients.”[48] Since the biocompatibility review did not reveal any new risks and since there were no changes to the product or its intended use, apart from color, Ethicon Norderstedt determined that its previous risk assessments for TVT clear were also applicable to TVT Blue.[49]

To ensure usability of the new-blue mesh device, Ethicon conducted clinician focus assessments, cadaver study and animal implant testing. These results were reviewed by the Norderstedt design team as part of the design validation process.[50] It is my opinion, based on my examination of the records provided, that Ethicon Somerville and Ethicon Norderstedt complied with applicable quality, safety and design process requirements and standards in the design and development of the TVT – blue.

Laser Cut Mesh

In 2005-2006, in response to customer requests, Ethicon undertook a project to introduce an additional variety of the TVT and TVT-O devices. The original mesh products were cut mechanically. It was determined that the process modifications to be made would increase product yields, reduce the cycle time and also possibly reduce fraying of the mesh.[51] The TVT

---

[45] ETH.MESH.10587971.
[46] ETH.MESH.02608167-ETH.MESH.02608169.
[47] ETH.MESH.02608132.
[48] ETH.MESH.02608170-ETH.MESH.02608171.
[49] ETH.MESH.10587931-ETH.MESH.10587950.
[50] ETH.MESH.10587905-ETH.MESH.10589323.
[51] ETH.MESH. .00309255, ETH.MESH.00309276-ETH.MESH.00309281.

Laser Cut mesh project produced additional documentation specific to the laser cutting process. It was determined that the laser cutting process modification required additional verification testing and risk assessment in order to meet design control requirements. These documents, among others, were added to the design files:[52]

- Device Labeling
- Finished Goods Specification
- Component Drawings
- Packaging Drawings
- Process Validations specific to the Laser Cut Mesh
- Risk Management Report - RMR-0000017
- Complaint Review for Risk Management Plan
- Design FMEA for Laser Cut Mesh Project
- Clinical Expert Report specific to Laser Cut Mesh
- Design Requirements Matrix
- Design Verification for TVT Laser Cut Mesh Sheath Removal CPC-2006-0134
- Design Verification for TVT Laser Cut Mesh CPC-2006-0102
- Design Verification of TVT Laser Cut Mesh - (Particle Loss) CPC-2006-0014
- Performance Evaluation of TVT Prolene Blue Mesh – Dated March 3, 2006

It is important to understand that often a change like the laser-cut option is initiated by customer request. Some physicians may not like the appearance of the mechanically cut edges of the mesh, while others may prefer mechanical cut mesh, which is still offered and even preferred today. For example, while some surgeons prefer the TVT and TVT-O Laser cut products, the majority still prefer the mechanically cut TVT and TVT-O products.[53] Such customer preference changes do not suggest any thing is wrong with the product. (Of course when a corrective action requires a manufacturing or design change, Ethicon has demonstrated it will promptly make those adjustments.) But sometimes minor product changes are just because of customer requests, as long as they do not introduce new safety issues of course. Because customer-inspired changes require just as much verification and validation as original designs, it is not common to see cosmetic changes made to medical devices.

COMPLAINTS, RISK MANAGEMENT and CAPA

It is my conclusion after reviewing records of complaints, risk management assessment (including DDSA) and CAPA (Corrective and Preventive Action) records that Ethicon followed its procedures, which met or exceeded the industry practice, to evaluate, investigate and report customer feedback. These efforts were not isolated but rather were integrated across many departments involving personnel with many talents and experience.

With respect to each of the complaints and CAPAs that I reviewed, Ethicon demonstrated that appropriate decisions to trend complaints or initiate CAPAs were made. For anyone without a medical device background it is not very clear how much analysis takes place. An auditor knows

[52] ETH.MESH.00309254-ETH.MESH.00309350; ETH.MESH.06695482-ETH.MESH.06698795.
[53] Exhibit T-3599; Exhibit T-3600.

to not look at just one file, or even one group of files (say complaints) to understand the integrated analysis that takes place.

First, the field report is examined to determine whether the allegation is against the product or not, because sometimes field reports do not even involve an Ethicon product. Complaints that need to be investigated for more information or to clarify a report may take days, weeks, or even months to run down. Calls to doctors, field reps or even sometimes patients are required. If a complaint even suggests a serious injury the investigator is under a deadline to make a decision to report to the various national and international databases, sometimes before all the facts can be gathered. If the complaint is valid, part of the investigation involves pulling records from the Device History Record to determine if final quality inspections had detected any issues with the lot. If the lot and complaint validity cannot be verified, the complaint may be closed, and reopened later if a device is returned or more information is provided. When the complaint is fully investigated the determination for whether to "trend" the complaint or take continuing action is made. Usually a particular type of complaint must become frequent enough to demonstrate a statistical trend or rise above the known frequency of occurrence before a corrective action can be taken because of the scope of understanding required to decide the action, effectuate the action and then monitor the effectiveness of the action. This is because a root-cause analysis is required before anyone should attempt to correct what could be an anomaly. This is also because the medical industry appreciates that random and excessively zealous changes can cause unanticipated consequences. As explained below, Ethicon has demonstrated effective response to complaints that have led to corrections at the design, manufacturing, and communication levels since the inception of the TVT. Here are some examples of how Ethicon has performed these responsibilities, particularly during the very time Ms. Wilson claims otherwise.

- In June 2000, Ethicon reviewed the then-reported side effects associated with the use of TVT, determined that the risk of serious complications was quite low and concluded that the benefits of TVT greatly outweigh any risks.[54] During the latter part of 2000 and continuing through all of 2001, Ethicon continued to trend TVT complaints quarterly broken down by types of medically related complaints, assembly complaints, and needle pull off complaints.[55]
- A July 2000 complaint report demonstrates that Ethicon investigated a report of a twisted mesh that was identified prior to a procedure.[56] Ethicon's investigation into this report included a review of the circumstances surrounding the twisted mesh and a physical evaluation of the device in question. In May of 2001 a CAPA was initiated to review this mesh twist complaint.[57] The CAPA confirmed the twisting of the mesh and provided a "Risk Analysis Summary" that stated "Since this is (sic) first complaint of this kind, we are unable to conclude any cause. At this point, no corrective action will be taken unless a trend is developed."[58] Thereafter, in June of 2001, this CAPA was closed.

[54] ETH.MESH.06852214-ETH.MESH.06852217.
[55] ETH.MESH.19762712-ETH.MESH.19762717; ETH.MESH.19762721-ETH.MESH.19762725; and ETH.MESH.19762729-ETH.MESH.19762734.
[56] ETH.MESH. 02620955-02620959.
[57] ETH.MESH.05961854-05961859.
[58] ETH.MESH. 05961856.

- In May 2001, Ethicon instigated a CAPA analysis regarding a needle pull off.[59] In this CAPA, Ethicon reviewed Medscand Medicals previous analysis of this issue.[60] Thereafter, Ethicon integrated Medscand Medical's corrective actions and implemented its own CAPA analyses to address the pull off issue. The CAPA concluded with the "corrective action" of continuing to monitor new devices produced via a new manufacturing process.[61] This CAPA generated a run of a new manufacturing process to address the needle pull off issue that was subsequently instituted and monitored by Ethicon.[62] This is another example of how Ethicon properly implemented its CAPA procedures, considered the previous analysis of Medscand, and then continued to monitor the corrective action until effectiveness data demonstrated that they could close the CAPA.[63]
- In June 2001, Ethicon convened an internal team to again formally discuss the then known medically-related complaints to date.[64] They determined that these complaints were not extraordinary and are common in most procedures of this type. They concluded that they only needed to continue monitoring complaints.
- In another complaint report dated October 2001, Ethicon investigated a report about a TVT mesh that had an uneven width and frayed edges.[65] The information showed the issues with the mesh were discovered prior to usage, and had no impact on the procedure. Nevertheless, the complaint report demonstrates that Ethicon investigated the complaint via interviews and device evaluation from October of 2001 to July of 2002. Thereafter, Ethicon opened a CAPA to confirm and develop risk conclusion for the October 2001 fraying complaint.[66]
- In December 2001, Ethicon's Medical Director reviewed all of the complaints for 2001, totaling less than 58 patients for a complaint rate of 0.44 per 1000 TVT units sold that year.[67] The review found no pattern that would suggest any medical issues with the TVT product. In February 2002, Ethicon again reviewed the complaints through 2001 and did not find need for further action.
- Ethicon's Sue Meltzer authored a "Device Design Safety Assessment (DDSA) Re-Evaluation for TVT" in April 2002.[68] Ms. Meltzer identified what she described as eleven new categories of hazards that were not described in the "Preventia" risk assessment from July 2000 Revision 8. While Ms. Meltzer concluded that this prior risk assessment needed to be updated, I am not surprised that there was nothing in the file as a "follow-up" to the memo because, as noted previously, engineers at Ethicon GmbH prepared an updated risk assessment in May 2001 that already addressed the hazards

[59] ETH.MESH.05961860 -05961869.
[60] ETH.MESH. 19763198-19763199.
[61] ETH.MESH. 05961863.
[62] ETH.MESH. 05961871.
[63] ETH.MESH.05961866.
[64] ETH.MESH.08687705-ETH.MESH.08687707.
[65] ETH.MESH.02622357-ETH.MESH.02622363.
[66] ETH.MESH.05961204-ETH.MESH.05961211.
[67] ETH.MESH.03716322-ETH.MESH.03716326.
[68] ETH.MESH.01317510-ETH.MESH.01317524.

listed in her memo in April 2002.[69] These hazards were not "new", were already well known prior to 2002, and had already been evaluated. Moreover, some of these hazards had even appeared in Ethicon's IFU in effect since 1999.[70] As early as June 2000, a panel of 17 surgeons experienced in the use of TVT discussed the then-known hazards associated with the clinical use of the TVT mesh and concluded they were minimal.[71] In addition, in December 2001, Ethicon's Medical Director, Martin Weisberg, M.D. had yet again assessed the then-known risks associated with the product.[72]

- In December 2003, Ethicon's medical director prepared a clinical expert report specific to the TVT-O device which concluded that it would be safe and effective.[73] At that time, Ethicon also obtained a performance report on TVT-O in which five physicians participated in the study.[74]
- In July 2004, Ethicon performed a post-launch review of TVT-O.[75] No new hazards were revealed and the reported complaints were within the predicted range. No further action was required.
- A review of complaints for the first 10 months of 2005 found again only relatively few reports of the same types of complaints found in the earlier reports discussed above.[76]
- In February 2006, Ethicon conducted a comprehensive review of all TVT and TVT-O complaints for the entire period from August 2003 through January 2006.[77] Of all medically-related complaints the highest category was 0.011%, or just 15 complaints out of a total of 137,378 TVT products sold during that time. Ethicon used this complaint analysis to perform a new risk assessment for the TVT product with the only product change being to add the laser cut variety.[78] The risk assessment confirmed that the overall residual risk remained acceptable.
- In April 2006 Ethicon prepared a clinical expert report for laser cut TVT and TVT-O which determined that the laser cut mesh would not present clinically significant differences from the mechanically cut mesh.[79]
- In 2006 Ethicon prepared RMR-0000017, a risk management report for the laser cut TVT and TVT-O which determined that the overall residual risk was acceptable.[80]
- Ethicon performed another complaint review for the period from January 1, 2006 to June 2008, which again did not indicate any reason for any further risk assessment.[81]

---

[69] ETH.MESH.10587932-ETH.MESH.10587939.
[70] ETH.MESH.10591676- ETH.MESH.10591681.
[71] ETH.MESH.10027307-ETH.MESH.10027328.
[72] ETH.MESH.03716322-ETH.MESH.03716326.
[73] ETH.MESH.02128955-ETH.MESH.02128966.
[74] ETH.MESH.02128967-ETH.MESH.02128982.
[75] ETH.MESH.00259447-ETH.MESH.00259447.
[76] ETH.MESH.09498446 (PowerPoint version).
[77] ETH.MESH.15055884-ETH.MESH.15055886.
[78] ETH.MESH.00309259-ETH.MESH.00309264.
[79] ETH.MESH.00309275-ETH.MESH.00309281. Complaint investigations may have limited access to surgical history when a patient presents with an adverse condition after hospital discharge. Thus, it can be difficult to locate surgical method details such as whether the surgery was TVT or TVT-O. By ensuring that all uses of the TVT mesh are viewed within the same complaint and risk analysis system, Ethicon was helping ensure continuity within the common product experience.
[80] ETH.MESH.10618731-ETH.MESH.10618735.

- In 2008, Ethicon undertook a Risk Management Report, RMR-0000044, which analyzed yet again the potential harms resulting from the TVT and TVT-O procedures and the associated hazards that could potentially cause the harm. The resulting risk was in all cases acceptable.[82]
- In May 2010, Ethicon performed another complaint review of the TVT product for the period from January 2008 through December 2009.[83] Again, there were no new indicators of any need for a new risk assessment.
- In August 2010 Ethicon prepared a clinical evaluation report for the TVT device with abdominal guides.[84] Given that the mesh device was the same as for TVT, another complaint review of the TVT device was made, this time covering the period from January 2006 through December 2007. The report again demonstrates that no new risk assessment was needed.
- In August 2010 Ethicon prepared a separate clinical evaluation report for TVT-O.[85] The report included a detailed review of the clinical literature from 2004 through early 2010 as well as review of the complaints reported for 2006 and 2007. No new risks were observed and the reported complaints were within the predicted range. Ethicon performed a benefit-risk analysis in accordance with ISO 14971:2007 that again determined that the benefits of TVT-O outweigh the observed risks.
- In November 2010 Ethicon issued an update to RMR-0000044, the risk management report for TVT and TVT-O which again determined that the overall residual risk remained acceptable.[86]
- In November 2010 Ethicon issued an update to RMR-0000017, the risk management report for laser cut TVT and TVT-O which again determined that the overall residual risk remained acceptable.[87]
- In 2013 Ethicon prepared another clinical evaluation report for the entire family of TVT products. The report includes a review of all complaints for the period from January 2010 through January 2013.[88] The analysis verified that there were no new risks and that the current risks remain within acceptable levels.

Based on my review of all of the foregoing complaint report reviews, clinical expert reports, risk management reports and the applicable CAPA reports, it is my opinion Ethicon properly applied its resources to obtaining feedback from some of the most experienced physicians, monitored complaints and MDRs, conducted research and made efforts for continuous product improvement to meet the needs of the users and patients as the science and medical practice in the applications of surgical mesh to urinary incontinence evolved. In my opinion, based on my review of the documents provided to me, from the time of the licensing of TVT, Medscand and then Ethicon, robustly complied with applicable industry regulations and standards in the design,

---

[81] ETH.MESH.06852419-ETH.MESH.06852421.
[82] ETH.MESH.10618793-ETH.MESH.10618806.
[83] ETH.MESH.01593047 (Word Doc. version).
[84] ETH.MESH.00353635-ETH.MESH.00353674.
[85] ETH.MESH.06403140-ETH.MESH.06403180.
[86] ETH.MESH.10618793-ETH.MESH.10618806; ETH.MESH.10618812-ETH.MESH.10618814.
[87] ETH.MESH.10618741-ETH.MESH.10618746; ETH.MESH.10618753-ETH.MESH.10618756.
[88] ETH.MESH.10178882-ETH.MESH.10179216.

development and marketing of the TVT and TVT-O products using both mechanically cut and laser cut mesh.

REBUTTAL TO OPINIONS OF ANNE WILSON IN HER REPORT DATED 2016.01.30

I have previously issued a report that included a rebuttal to opinions expressed by Ms. Wilson in her earlier report dated 2015.08.24 concerning the TVT product. Ms. Wilson's current report has either omitted or changed a number of her previous opinions and discussions. I will limit this rebuttal to responding to her current report with the understanding that I stand by my previous rebuttal to the extent Ms. Wilson may revive any of her former opinions and discussions concerning TVT. However, I may comment concerning some of her former opinions and discussions in order to put her current report in proper perspective. To the extent Ms. Wilson's current report repeats any of her prior opinions and discussion, I will likewise incorporate my responses along with my responses to her new opinions.

I would also note at the outset that in this report the absence of a comment concerning a statement by Ms. Wilson should not be interpreted as an agreement with her statement. As a certified auditor, Ms. Wilson must be accurate in her citations and must view the facts with an unbiased eye. An auditor has the responsibility to follow a **s**ystematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled. Even though she has attempted to characterize her report as not being an audit, the ethical requirements are still applicable. I have observed that Ms. Wilson repeatedly misstated the contents or context of documents that she reviewed. There are instances when information was contrary to her position and she omitted it. Finally, there are key documents that Ms. Wilson either was not provided or that she ignored. I will demonstrate a few examples of how her report is:

> biased and inaccurate by failing to discuss documentation opposed to her opinions (e.g., Ethicon's biocompatibility analyses and the FDA's own biocompatibility assessment);
>
> in some cases invoking standards that did not apply at the time of the events she was discussing (e.g., her use of standards to analyze different risk assessments over a ten-year period);
>
> in some cases not based upon any foundation (e.g., her discussion of degradation);
>
> incorrectly applies applicable standards (e.g., misusing the terms "risk" and "failure modes")
>
> is contrived to besmirch the Ethicon quality program.

Comments Concerning Ms. Wilson's Summary

Ms. Wilson first opined that Medscand/Ethicon failed to comply with requirements for a "cohesive risk management system." I disagree for several reasons. First, there is ample evidence that Medscand did in fact adopt and document proper QMS activities for the original

TVT.[89] Second, there is ample evidence that Ethicon maintained a thorough risk management system for TVT and TVT-O.[90] Third, Ethicon's properly applied industry standards and internal procedures in "leveraging" its extensive knowledge of both Prolene and TVT in the design and development of TVT-O.[91] Fourth, I find that Ethicon did in fact properly "take into account the unique applications" for TVT-O as well as important knowledge gained from TVT to develop TVT-O.[92] Fifth, Ms. Wilson's opinion that the "use" of TVT-O is "unique", and thus different from TVT, is wrong. In fact, the obturator approach was already in use by surgeons, but they did not have the specialized tools that became part of TVT-O.[93]

Next, Ms. Wilson criticized Ethicon's risk analysis *procedures*, but I find the *procedures* to have properly implemented medical device risk analysis and risk management practices as they evolved in practice through the industry.

Finally, Ms. Wilson opined that Ethicon's risk management was inadequate for TVT-O, but I found that its risk management was thorough and in accordance with medical industry standards.

Comments Concerning Ms. Wilson's Discussion of Relevant Standards

a. MIL-Q-9858A

MIL-Q-9858A was a military specification concerning quality management of military contracts dating back to the 1950s.[94] These specifications were roughly equivalent to the FDA's good manufacturing practices, or GMPs. Neither the GMPs nor these specifications addressed design controls, risk analysis, risk assessment, risk management and a variety of other elements of quality systems management introduced later in both the FDA's QSRs and ISO 13485. In short, Ms. Wilson had no basis for opining that MIL-Q-9858A was ever a required standard for medical device manufacturers. Ms. Wilson cannot possibly apply this military standard in her work with medical device companies. Again, this military standard does not even address the design control issues and risk management issues that are the subject of her report. Moreover, these standards were obsoleted in 1996.

b. ISO 9001

ISO 9001:1994 was not only non-industry specific as Ms. Wilson acknowledged, but it certainly was not mandatory for the medical device industry. ISO 9001:1994 set forth suggested quality

---

[89] ETH.MESH.10184398-ETH.MESH.10184408; ETH.MESH.10184418-ETH.MESH.10184423; ETH.MESH.01316731; ETH.MESH.01317609-ETH.MESH.01317613.

[90] See the section above under the heading "Complaints, Risk Management and CAPA."

[91] See 21 CFR Part 820; FDA guidance documents such as FDA Program Memorandum G95-1; EN 1441; ISO 14971:2000; ISO 10993; and PR602-003, ETH.MESH.10619580-ETH.MESH.10619604 (Rev. 5).

[92] ETH.MESH.00259047-ETH.MESH.00260002 (Book 1); ETH.MESH.01317769-ETH.MESH.01318358 (Book 2); ETH.MESH.01804278-ETH.MESH.01804592 (Book 3); ETH.MESH.01318359-ETH.MESH.01318831 (Book 4); ETH.MESH.00222779-ETH.MESH.00223267 (Book 5); ETH.MESH.01318832-ETH.MESH.01319499 (Book 6); ETH.MESH.01319500-ETH.MESH.01320123 (Book 7); ETH.MESH.22134203-ETH.MESH.22134747 (2003 Technical File).

[93] ETH.MERSH.03932909-ETH.MESH.03932911.

[94] http://www.expresscorp.com/media/pdf/specs/MIL-Q-9858A.pdf.

systems provisions that a contracting party could consider requiring its suppliers to meet. ISO 9001:1994 did not address the risk analysis, risk assessment and risk management issues discussed in Ms. Wilson's report. Moreover, it did not reference EN 1441 or ISO 14971.

d. ISO 13485

ISO 13485:1996 is another operational standard for quality systems relating to medical devices. ISO 13485 was not approved as the standards for medical device quality systems management in Europe until the 2003 version, ISO 13485:2003. In the United States, ISO 13485 compliance has never been recognized as a substitute for compliance with 21 CFR Part 820 regarding quality systems management requirements.

Ms. Wilson opined that ISO 13485:1996 was a risk analysis standard. It was not. It did not even reference either EN 1441[95] or ISO 14971 (which are risk analysis standards discussed below) until the revision of ISO 13485 in 2003: seven years after Ms. Wilson states. Furthermore, for the CE Mark, EN 46001 was not obsolete until about 2004 with the adoption of ISO 13485:2003. Thus, certification to EN 46001 was accepted until that time, although many ISO registrars began to assert certification to ISO 13485 for their own convenience prior to this date. Likewise, Ms. Wilson's statement linking ISO 13485 to ISO 14971 also neglects that in Europe ISO 14971 was not approved by CEN/CENELEC until 2003, more than seven years after she suggests that its "requirements" should have been implemented by Ethicon.[96] Again, therefore, Ms. Wilson neglects that Ethicon was in compliance with the then-applicable standards; and she improperly believes that Ethicon should have complied with standards that did not yet exist. Finally, conformity to the applicable standards at any given point in time is best assessed and concluded not by Ms. Wilson, or even myself, but rather by the third party inspectors and auditors of the FDA and Notified Bodies (BSI, TUV and Danish Standards Association) who were charged with the duty to certify compliance with the standards first hand reflecting the then current interpretation of those standards and best practices.[97]

f. ISO 14971

ISO 14971 is a standard for risk management that has evolved over time and on the experience gained from EN 1441. The first version to become a requirement in Europe was ISO 14971:2000 which was not adopted by CEN/CENELEC until 2004. The focus of much of Ms. Wilson's report appears to be on ISO 14971:2007. However, she gives the misleading impression that this version of ISO 14971 applied at an earlier time in many places. This is not so.

---

[95] BS EN 1441 is the UK adoption of EN 1441 which did not include provisions for life-cycle risk management, only design risk analysis.

[96] ISO 14971 introduced "risk management" in the 2000 edition, but did not emphasize risk management until the 2007 edition when it became Annex B.

[97] See, e.g., ETH.MESH.22134251-ETH.MESH.22134263; ETH.MESH.02781437-ETH.MESH.02781458; ETH.MESH.02252211-ETH.MESH.02252224; ETH.MESH.10589770; ETH.MESH.10586755-ETH.MESH.10586758.

It is critical to understand that the US FDA has recognized the 2007 version of ISO 14971, and not the more recent 2012 version. Even more importantly, (even though recognized as a consensus standard in some respects) ISO 14971:2007 compliance is not required by FDA unless specifically directed. In the United States, the standard set by the FDA regulation requires that risk analysis be performed—not that it be performed to ISO 14971 or by any specific method or format. Ms. Wilson's opinion that ISO 14971 is "non-optional" is incorrect in the United States. Even in the EU not all companies produce an aFMEA, dFMEA, pFMEA or sFMEA, Ms. Wilson's opinion to the contrary notwithstanding. Furthermore, various risk analysis methods use spreadsheets for documentation purposes and may only appear to be an "FMEA."

Ms. Wilson is correct that ISO 14971 standard is more prescriptive than ISO 13485 and specifically calls for a risk management plan; risk management procedure; and residual risk evaluation and overall residual risk evaluation. Ms. Wilson quoted an excerpt from the standard in opining that a "key concept" is that of risk. However, Ms. Wilson distorted the standard's intent by avoiding the next sentence which states:

> The acceptability of a risk to a stakeholder is influenced by these components (referring to probability of harm and severity) *AND BY* the stakeholder's perception of the risks.

The standard's introduction goes on to recognize that stakeholders include medical practitioners, the organizations providing health care, governments, industry, patients and members of the public.

g. FDA's QSRs

My understanding is that Ms. Wilson's report is intended for use in litigation over TVT-O devices marketed in the United States. However, her report ignored the industry standards for quality systems and risk management applicable in the United States, that is 21 CFR Part 820 and the various guidance documents issued by the FDA, including the FDA's General Program Memorandum G95-1, Recognition of Consensus Standards, Design Control Guidance for Medical Device Manufacturers, Use of Standards in Substantial Equivalence Determinations, Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, guidance regarding Medical Device Use-Safety, Guide to Inspection of Quality Systems and the FDA's various guidances for benefit-risk assessments, to name just a few.[98] It is telling that Ms.

[98] http://www.fda.gov/RegulatoryInformation/Guidances/ucm080735.htm; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077274.htm; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm; http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073756.pdf; http://www.fda.gov/RegulatoryInformation/Guidances/ucm073790.htm; http://www.fda.gov/downloads/MedicalDevices/.../ucm094461.pdf; http://www.fda.gov/downloads/ICECI/Inspections/UCM142981.pdf; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm282958.htm; http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf;

Wilson ignored all of these guidances, but in her separate TVT report chose to cite guidance from the European regulators.[99] In short, much of Ms. Wilson's report is not based upon United States requirements for medical device manufacturers. Ms. Wilson's repeated mischaracterization of voluntary standards as "non-optional" clouds the true picture of the product development environment for products sold in the U.S. The true picture is much more nuanced and complex than one international standard that has not even been adopted by the U.S. to this day.

h. ISO 10993

Given that Ms. Wilson chose to opine regarding degradation, she completely ignored the most relevant standard. ISO 10993, and its various subparts, address the biological evaluation of medical devices. These standards are recognized with some reservations, a few worthy of mention below, as voluntary consensus standards in the United States. The standards specifically address how medical device manufacturers are expected to satisfy concerns over biocompatibility. This includes any concerns over chemical degradation such as oxidative degradation (such as in ISO 10993-9). Ms. Wilson expressed opinions concerning degradation of Prolene, yet her report totally ignored, and did not even reference, ISO 10993. Ethicon complied with ISO 10993 in its biocompatibility risk assessments for its Prolene mesh used in TVT and TVT-O. Ms. Wilson's opinion that degradation was a "critical risk ignored by Ethicon" is clearly an uninformed opinion since she: (1) failed to apply the appropriate standard in formulating her opinion, (2) failed to include an analysis of Ethicon's biocompatibility risk assessments for Prolene mesh and systems dating back to the 1990s,[100] and (3) failed to consider the FDA's own 1990 biocompatibility assessment of polypropylene in general as an implant material.[101]

Comments Concerning Ms. Wilson's Discussion of Risk Planning Using FMEA Analysis

Ms. Wilson acknowledged that: "*Although no specific risk acceptability levels are prescribed, each company is required to responsibly define their criteria for acceptability within the plan and ensure that a process is in place to apply and assess risk control measures. The medical benefit after application of risk control measures must outweigh the residual risk. This is classic risk-benefit analysis. Key to this analysis (the "risk") is actual occurrence of patient **harm**.*" However, her subsequent opinions ignored these very principles. For example, Ms. Wilson opined that Ethicon's risk analyses are deficient with respect to degradation, but she failed to identify any harm associated with degradation.[102]

---

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM451440.pdf.

[99] MEDDEV 2.12-1 Guidelines on Medical Device Vigilance System (January 2013).

[100] ETH.MESH.06398824-ETH.MESH.06398918; ETH.MESH.16046471-ETH.MESH.16046531; ETH.MESH.22007390-ETH.MESH.22007391; ETH.MESH.00349224-ETH.MESH.00349237.

[101] ETH.MESH.06934664-ETH.MESH.06934688.

[102] Another "key" that Ms. Wilson failed to mention or to identify was a "failure" of TVT or TVT-O to meet any of its performance requirements as a result of degradation.

Ms. Wilson initially acknowledged that the FMEA approach is merely one risk analysis tool. Yet her report later argued that any variance from her view of either what a design FMEA should encompass or how to document risk assessment activities means there is a lack of compliance with standards. The medical industry standards to which she referred do not specify the details as to how a manufacturer must perform or document risk assessment activities. For example, ISO 14971:2007 Annex G lists several examples, but, as the standard states, even this list is not exhaustive but rather discusses "some" of the available techniques.[103] Ms. Wilson stated that a design FMEA is a "living document" that must be updated as soon as new information is received. That is not accurate. For example, other methods of risk assessment may be more efficient for post market surveillance because the emphasis must shift to isolating the root cause of the observed or reported complaint. (A design FMEA or process FMEA may need to be updated to incorporate new understandings before implementing a product change.)

Ms. Wilson opined that in the context of a design FMEA "[f]ailures are any errors or defects . . . ." Such a broad, sweeping statement is not correct. The analysis of "failure" refers to the medical device or its components failing to meet one or more of the stated design requirements. In point of fact, the one time when the FDA questioned Ethicon's complaint management, the FDA wanted to make sure that Ethicon put into its procedures to document that they had confirmed during the complaints investigation that the product met its quality specifications.[104]

Ms. Wilson correctly acknowledged that the use of any medical device entails at least some degree of risk. This acknowledgement is inconsistent with opinions she expressed later in her report that appear to be based upon a premise that all risks must be eliminated.

Comments Concerning Ms. Wilson's Discussion of Ethicon's Internal Standards

Ms. Wilson correctly observed that Ethicon's internal procedures are written to comply with the international standards adopted in Europe. This should be expected because Ethicon also markets its products in Europe and other countries such as Canada. Since her report is intended for a United States audience, Ms. Wilson should have observed that Ethicon's internal procedures are also written to comply with the FDA's QSRs and other FDA guidance documents. I have identified Ethicon's procedures at the time of the TVT-O design elsewhere in this report.

Comments Concerning Ms. Wilson's Discussion of "Risk Management System Failure"

Ms. Wilson's first opinion in this section of her report was that Ethicon "did not adequately identify, analyze, and mitigate all known risks associated with the TVT-O device." However, she failed to identify any such risks. Ms. Wilson's failure to identify the risks that she believes were not addressed leaves her opinion baseless. Moreover, the decision regarding the means and extent to which a specific risk may be mitigated is beyond the scope of the standards on which Ms. Wilson relied.

---

[103] See ISO 14971 at p. 56.

[104] ETH.MESH.02781437-ETH.MESH.02781458. On a separate note, this analysis also applies to another part of Ms. Wilson's report where she opined that FMEAs must be updated. The FDA did not require an updated FMEA in response to complaints.

Ms. Wilson made a statement that implies that Ethicon "consider[ed] the TVT-O to be the 'same' as the TVT-R." This is a gross mis-statement. In my opinion, Ethicon's design history files and technical files for TVT-O show extensive work that Ethicon performed to identify and assess the actual differences.[105]

Ms. Wilson expressed the opinion that "it is more important to look at the differences between the systems [i.e. TVT versus TVT-O] and ascertain what the appropriate risk management activities should be." I absolutely agree with this opinion. That is what ISO 14971 contemplates the manufacturer will do. Ms. Wilson did not explain why this principle is important. It may seem intuitively obvious, but the standard does not leave it to intuition. The standard recognizes that when a design change is being made to an existing marketed device, there may be little reason for a manufacturer to conduct a new risk analysis on aspects of the device that are not being changed. As I have previously observed, ISO 14971 states:

> **4.1 Risk analysis process**
>
> Risk analysis shall be performed for the particular medical device as described in 4.2 to 4.4. The implementation of the planned risk analysis activities and the results of the risk analysis shall be recorded in the risk management file.
>
> NOTE 5 The scope of the risk analysis can be very broad (as for the development of a new device with which a manufacturer has little or no experience) or the scope can be limited (as for analysing the impact of a change to an existing device for which much information already exists in the manufacturer's files).

It is my opinion that Ethicon's design history files and technical files for TVT-O, including but not limited to the Device Design Safety Assessments, show that Ethicon did in fact place its emphasis on the differences between TVT-O and TVT, including those listed by Ms. Wilson.[106]

It is important to understand that the TVT-O design team documented from their first risk analysis review meeting (the TVT-O DDSA Rev. 0) that the focus of the team's efforts had to be on the usability of the new instrumentation and capturing all important aspects of the differences in the clinical procedure: since this was in fact the reason for the TVT-O.[107] The team in fact did follow a "systematic approach" but used a different method than a dFMEA as their focus for risk management for the device changes, which is allowed within ISO 14971. Such an example is when it is evident that Human Factors will be the most important element of the design change.[108] I see this to have been the strength of this experienced design team.

---

[105] ETH.MESH.00259047-ETH.MESH.00260002 (Book 1); ETH.MESH.01317769-ETH.MESH.01318358 (Book 2); ETH.MESH.01804278-ETH.MESH.01804592 (Book 3); ETH.MESH.01318359-ETH.MESH.01318831 (Book 4); ETH.MESH.00222779-ETH.MESH.00223267 (Book 5); ETH.MESH.01318832-ETH.MESH.01319499 (Book 6); ETH.MESH.01319500-ETH.MESH.01320123 (Book 7); ETH.MESH.22134203-ETH.MESH.22134747 (2003 Technical File).

[106] ETH.MESH.00259416-ETH.MESH.00259445 (Rev. 0); ETH.MESH.02259448-ETH.MESH.02259472 (Rev. 1); ETH.MESH.02259474-ETH.MESH.02259501 (Rev. 2).

[107] ETH.MESH.00259416-ETH.MESH.00259445.

[108] http://www.fda.gov/downloads/MedicalDevices/.../ucm094461.pdf. FDA guidance on using human factors in risk analysis.

Ms. Wilson opined that Ethicon relied on a "2001 dFMEA"[109] for its risk assessment of the differences between TVT and TVT-O. That is not at all what Ethicon did. Ethicon performed new risk analyses on the aspects of TVT-O that differed from TVT. The TVT-O design history files and technical files plainly show that Ethicon relied on the "2001 dFMEA," other prior risk analyses and its extensive post-market surveillance experience only for the components common to both TVT and TVT-O, not the aspects that were different.

Ms. Wilson opined that Ethicon's "2001 dFMEA was inappropriate because it is based on pre-market data and contains contradictions and omissions." I have three serious disagreements with her opinion concerning Ethicon's "2001 dFMEA." First, in my opinion this risk analysis produced by the design team in Germany, Ethicon GmbH in May 2001 and approved by executive management, was compliant with EN 1441, the applicable standard at the time.[110]. Second, I am amazed that Ms. Wilson would criticize a dFMEA for being based on pre-market data. Design FMEAs by their very nature are typically based on pre-market data. Third, Ethicon's design history file and post-market surveillance records plainly show that the "2001 dFMEA" was not based solely on pre-market data, but rather did in fact assess hazards and harms reported in post-market surveillance data during years of marketing the product in Europe and the U.S.

I believe it is important to understand that Ethicon has been audited many times. In another report Ms. Wilson acknowledged that a series of audits over time reveals a "balanced picture of overall adherence to quality management system and operational practices." That is precisely one of the reasons it is important to understand that Ethicon's quality systems, including risk management, for its TVT products have been inspected by FDA auditors and European notified body auditors many times at multiple facilities over the years. I know of no medical device manufacturer who is 100% compliant 100% of the time.[111] For example, Ethicon conducted an internal audit in 2010 concerning its risk management process.[112] In my opinion, this audit is a good example demonstrating Ethicon's diligence in correcting an error in a risk management record. The audit reviewed some of the risk analyses for TVT and a number of Ethicon's other Prolene mesh devices. The audit report found some errors that needed correction, but did not result in a need to further assess any risks of TVT or any of the other Prolene meshes included in the review.

It is my opinion, based on the documents I reviewed, that Ethicon, and its TVT product quality program in particular, have an excellent overall audit record while TVT has been marketed for some 18 years. Audits are very important tools for reviewing compliance with industry standards, especially from a historical standpoint. Unlike both Ms. Wilson and myself, the auditors were there at the time events transpired, were presumably aware of the standards and issues of concern at the time, and conducted their jobs in a professional manner as evidenced by

[109] ETH.MESH.10587932-ETH.MESH.10587950.
[110] ETH.MESH.10587932-ETH.MESH.10587939.
[111] ETH.MESH.07281437-ETH.MESH.07281458; ETH.MESH.02252211-ETH.MESH.02252224. These FDA inspection reports show that Ethicon is not perfect. However, they also demonstrate thorough reviews of Ethicon's post-market risk management and the absence of need to reassess the overall residual risks of the TVT family of products.
[112] ETH.MESH.02252265-ETH.MESH.02252277.

their certifications and detailed reports.[113] The absence of any findings of shortcomings in the overall risk assessments of TVT or TVT-O by Ethicon's internal audits or the inspections by FDA and notified body auditors over these many years on the market speaks volumes about the quality of Ethicon's risk assessments for TVT and TVT-O.

Comments Concerning Ms. Wilson's Discussion of the TVT-O DDSA

Ms. Wilson opined that in Ethicon's risk analysis for TVT-O "[n]o part of the mesh was included despite the fact that the attachment mechanism and delivery method had changed." This is an example of Ms. Wilson's attempt to confuse. The purpose of the DDSA was to evaluate the differences between TVT and TVT-O. That does not mean that the team did not consider the mesh in relation to the instruments. The TVT-O DDSAs and other risk assessment activities documented in the TVT-O design history files did in fact include the attachment mechanism and delivery method because these were part of the changes discussed in the previous section.

Ms. Wilson opined that Ethicon's DDSA for the TVT-O device was deficient because "the scope is intended to be 'the medical device' rather than components." I disagree. This opinion directly contradicts both ISO 14971 and her own opinion in the preceding section of her report that when a design change is made, the focus is expected to be on the changes, not the aspects of the device that do not change.

Ms. Wilson implicitly criticized Ethicon's TVT-O DDSA by opining that the "DDSA does not require any rationale for the rankings given for the hazard or foreseeable failure defined in the standard [citing Section 4.4 of ISO 14971:2000]." I disagree. Both PR602-003[114] and the DDSAs themselves show the rationale that guided the team.

Next, Ms. Wilson opined that Ethicon's DDSA "did not require a detailed analysis" of each "failure/fault mode." In my opinion, Ethicon's DDSAs did in fact plainly show that the team properly evaluated potential failure modes of the aspects of TVT-O that changed from TVT, specifically those required to support the trans-obturator procedure.

Ms. Wilson opined that medical industry standards require a "system level" risk analysis. I disagree. Ms. Wilson did not define a "system level" analysis. The medical industry standards do not define a "system level" risk analysis. To the contrary, ISO 14971 explains that if a manufacturer chooses to use the FMEA format that Ms. Wilson prefers, then the "systematic approach" as stated by Ms. Wilson is performed for each "component." It is my observation that the team focused on "the system" which included the instrumentation in the hands of physicians performing the implant procedure. That is the most important system. Moreover, Ms. Wilson failed to identify any new hazards and harms that would have been identified in her theoretical "system level" analysis.

---

[113] See, e.g., ETH.MESH.22134251-ETH.MESH.22134263; ETH.MESH.02781437-ETH.MESH.02781458; ETH.MESH.02252211-ETH.MESH.02252224; ETH.MESH.10586944-ETH.MESH.10586946; ETH.MESH.10586748-ETH.MESH.10586749; ETH.MESH.10586755-ETH.MESH.10586758; ETH.MESH.10588872-ETH.MESH.10588876; ETH.MESH.10589770.

[114] ETH.MESH.10619580-ETH.MESH.10619604 (Rev. 5).

MS. Wilson's Table 1 failed to include a large portion of Ethicon's risk management, but is actually a good, but not exhaustive, listing of Ethicon's systematic and continuous compliance with industry risk management standards.

I disagree with Ms. Wilson's opinion that Ethicon's various risk analyses fail "to show the overall risk to the end user." That is precisely what Ethicon's various clinical expert reports and benefit-risk analyses do.

Ms. Wilson opined that Ethicon's risk management system was "unsound" and lacked a "functioning feedback loop." I disagree. Ethicon's functioning feedback loop entails constant post-market surveillance and periodic complaint reviews, complaint trending[115] and clinical expert reports (sometimes called clinical evaluation reports) that I have cited earlier in this report. This is the functioning feedback loop contemplated in Section 9 of ISO 14971:2007.

Ms. Wilson opined that "Ethicon did not include all known risks in their overall residual risk calculation" and that "many risks were not addressed." Again, she failed to identify the "risks" that she believes Ethicon omitted. Moreover, she referred to "their overall residual risk calculation," but she did not identify the calculation to which she referred. Ethicon has conducted multiple overall residual risks analyses on the TVT family of products.

Ms. Wilson's opinions leave the impression that Ethicon has refused to ever acknowledge and rectify any issues concerning the TVT and TVT-O devices. She is wrong. Ms. Wilson ignored that Ethicon did in fact mitigate complaints in the early versions of the product and listened to physicians about preferences and concerns and made modifications where appropriate. It is to be expected that complaints from the field would vary over time. The frequency and nature of complaints will shift as physicians learn how to use the product or attempt to use it beyond the methods described in the labeling. In my opinion, based on the documents I have reviewed, Ethicon has diligently analyzed and monitored its TVT and TVT-O products and made changes where appropriate as the clinical experience with these products has evolved.

Comments Concerning Ms. Wilson's Discussion of "Risk Analysis Implementation Failure"

Ms. Wilson's Tables 2 and 3, and her opinions concerning her Tables 2 and 3, are extremely misleading:

1. In my opinion it was improper for Ms. Wilson to attempt to compare the risk analyses listed in her Tables 2 and 3 that spanned a ten-year time period, which were conducted for different purposes, and which reflected the evolving understanding of the clinical condition to which the device is indicated.
2. Ms. Wilson's opinion that these analyses were all based upon the same ranking and procedure is wrong, which she would have known had she made herself aware of how Ethicon's risk management procedures kept up with the revisions of the various medical industry risk management standards and best practices.

[115] E.g., ETH.MESH.00330197-ETH.MESH.00330200. Complaint trending compares actual frequencies of complaints to the predicted frequencies, and the team determines if the residual risk is acceptable.

3. The face of the TVT-O DDSAs show that Ms. Wilson was wrong in expressing the opinion that a rating of "3" meant "insignificant or negligible impact." In fact, it meant:

PR602-003
CP2002ANS006
Appendix VII

RISK SEVERITY RANKING
Page 1 of 1

Score	Description
3 Major	♦ Product replacement is required to complete therapy / procedure (single use disposables), or product repair/replacement required before next therapy / procedure (reusables), and it is reasonable to assume that replacements are readily accessible without causing patient harm. ♦ Product failure causes reversible patient/user harm and/or discomfort; and/or addressing failure causes procedural time to be moderately increased.[1] ♦ Any harm induced by the product failure may be reduced by administration of pharmaceuticals not normally required for standard post-operative therapy, and/or alteration of the user's technique to compensate for product failure, and/or other medical/non-surgical intervention. ♦ The failure may induce increased tissue trauma, trauma to surrounding tissue, and/or the patient may experience increased discomfort/pain without being a safety or patient health concern.

Both Table 2 and Table 3 compared aFMEAs with dFMEAs. This was improper because aFMEAs and dFMEAs do not serve the same purpose. Tables 2 and 3 also improperly attempted to compare risk analyses that did not cover the same components. This again led to misleading comparisons. For example, her entries "Not included" misleadingly suggest that there was an erroneous omission when in fact there was no omission, but rather the hazard had already been addressed in an earlier analysis.

Ms. Wilson's Table 3 asserted that several entries such as fraying, roping and degradation were not considered in risk analyses. That is wrong. As explained elsewhere in this report, Ethicon did analyze these matters.

ISO 14971 does not include a method for making comparisons between risk analyses prepared at different times and for different purposes. If the intent of ISO 14971 had been to demand uniformity in the ranking of harms and hazards, then it would have defined a methodology required to be followed by all manufacturers perpetually. It does not. In fact, it notes that different methods may serve as a check on one another.

Comments Concerning Ms. Wilson's Discussion of 2004 Complaint Review

I have reviewed the Post-Launch risk analysis review for TVT-O that Ethicon performed in 2004.[116] I find that this assessment was performed in conformance to Ethicon's internal procedures and ISO 14971:2000. Ms. Wilson opined that Ethicon "simply accepted as a TVT-R issue" the complaint reports that related to the mesh. There is no reason mesh-related issues should be tracked separately for TVT and TVT-O. In fact, if mesh related issues had been

[116] ETH.MESH.00259447.

managed separately for the two devices, the result may have been different management approaches to the same problem I also disagree that Ethicon "simply accepted" anything. As I have explained elsewhere in this report, Ethicon had a thorough risk management process for the TVT and TVT-O devices. Medical industry standards do not require any action when post-market surveillance does not reveal new hazards, new harms, new severity of harm or new frequency of occurrence.

Comments Concerning Ms. Wilson's Discussion of 2006 Complaint Review

Ms. Wilson stated that the 2006 complaint review was the "second" complaint review. In fact, as I have previously detailed in this report, there had been many previous complaint reviews and other post-market surveillance for TVT and TVT-O.

Ms. Wilson asserted that TVT-O introduced new risks that Ethicon did not identify, consider, analyze and mitigate. I disagree. First, her opinion incorrectly assumes that mitigation was needed. For example, the QSRs acknowledge that not all complaints require investigation; sometimes the root cause is already known and/or the mitigation is already underway. Second, Ms. Wilson ignored that part of the complaint review process includes review of prior risk analyses to determine whether the actual occurrences of predicted harms were within the expected range. She also ignored that the field experience had been monitored for years and at each review occurrences of predicted harms continued to remain within the expected range. Moreover, the various risks had already undergone benefit-risk analysis and continued to undergo benefit-risk analysis.[117] These activities are what is called for in the applicable medical industry standards. Ms. Wilson grossly mischaracterizes Ethicon when she impugns that the company "waited on others" to do its job.

Comments Concerning Ms. Wilson's Discussion Concerning Ethicon's Legacy Risk Assessment

Ms. Wilson opined that Ethicon conducted risk analyses of TVT and TVT-O in 2007 and 2008 in "an effort to remediate the risk management files." Her use of the term "remediate" plainly was intended to suggest that Ethicon was trying to correct an error or deficiency in its previous risk analyses. This is another example of Ms. Wilson's distortion of the facts. These risk analyses of legacy products were conducted to carry out revised Ethicon internal procedures.

Ms. Wilson stated that Ethicon was "required to address known hazards, remediate them or change the labeling . . . ." Ethicon did address the known hazards. Presumably Ms. Wilson was referring to risk reduction, not hazard remediation. ISO 14971 speaks to risk reduction. Hazard

[117] ETH.MESH.06852215-ETH.MESH.06852217; ETH.MESH.19762712-ETH.MESH.19762717; ETH.MESH.19762721-ETH.MESH.19762725; ETH.MESH.19762729-ETH.MESH.19762734; ETH.MESH. 02620955-02620959; ETH.MESH.08687705-ETH.MESH.08687707; ETH.MESH.03716322-ETH.MESH.03716326; ETH.MESH.07226579-ETH.MESH.07226582; ETH.MESH.003300197-ETH.MESH.00330200; ETH.MESH.06852419-ETH.MESH.06852421; ETH.MESH.10618757-ETH.MESH.10618792; ETH.MESH.00309259-ETH.MESH.00309267; ETH.MESH.10618793-ETH.MESH.10618806; ETH.MESH.00353635-ETH.MESH.00353674; ETH.MESH.10178882-ETH.MESH.10179216 (2013 CER).

remediation is beyond the scope of the standard. However, the risk analysis did not find that any risks needed further reduction. Ms. Wilson's opinion that all known hazards need remediation (risks need reduction) is not correct. Moreover, she lacks the qualification to opine as to what hazards need remediation (which risks need reduction). ISO 14971 specifically emphasizes that all medical devices are associated with some level of risk and specifically declined to set standards for clinical decision making, acceptable risk levels, or how to do hazard remediation:

> All stakeholders need to understand that the use of a medical device entails some degree of risk.
>
> . . . .
>
> This International Standard does not apply to clinical decision making.
>
> This International Standard does not specify acceptable risk levels.

Moreover, the standard plainly recognizes that it is up to the manufacturer to use its sound judgment to determine whether a risk needs reduction:

> **6.1 Risk reduction**
>
> When risk reduction is required, risk control activities, as described in 6.2 to 6.7, shall be performed.

Even in cases where a risk needs reduction, but reduction is not practicable, then a benefit-risk analysis can be performed to assess whether the benefits of the device outweigh the residual risks.

> If, during risk control option analysis, the manufacturer determines that required risk reduction is not practicable, the manufacturer shall conduct a risk/benefit analysis of the residual risk (proceed to 6.5).

Ms. Wilson's opinion that Ethicon's legacy products risk analysis was flawed because TVT and TVT-O were assessed together is wrong. She said that TVT and TVT-O are "multiple design types." That is not correct. The TVT implant and the TVT-O implant are identical.[118] The only difference is the surgical procedure by which the material is implanted. Both implants are placed in the same anatomical location and serve the same purpose. I note that Ms. Wilson's report challenges the safety of only the Prolene mesh component of TVT. That is, her only specific "hazards", as she terms them, discussed in her report are degradation, roping, curling, deforming, fraying, particle loss and stiffness. There is absolutely no reason why TVT and TVT-O should not be assessed together, particularly with respect to aspects that are common.

Ms. Wilson's opinion that Ethicon's risk management report[119] concluded that there is "no associated harm" with abdominal pain, or vaginal erosion/extrusion simply shows that she does not understand how to read the report. She improperly cited just one page out of the report and took the content of the table out of context. The detailed analysis of the complaints which is summarized in the table clearly shows that Ethicon recognizes pain and vaginal erosion/extrusion

[118] ETH.MESH.00860239-ETH.MESH.00860310; ETH.MESH.05225354-ETH.MESH.05225385.
[119] ETH.MESH.10618757-ETH.MESH.10618806.

are harms. For example, the table shows that there were thirty-four complaint reports for vaginal extrusion and erosion. The table also shows that of these complaint reports, 33 were associated with pain and one was not. In fact, Ethicon assigned harm levels of 10 and 9 for these events (the two highest severity categories).

Ms. Wilson opined that Ethicon did not address all of the risks listed in Sue Meltzers' 2002 memo. I have already explained that Ethicon did in fact address the matters discussed in her memo.

Ms. Wilson criticized Ethicon's finding that no harm was associated with broken, frayed or kinked mesh, but she herself failed to identify any harm associated with these conditions.

Ms. Wilson criticized Ethicon's findings that the overall residual risks for TVT were moderate. She expressed her own opinion that the risks were not moderate. She did not to show that Ethicon failed to follow its procedure for determining overall residual risk levels or that Ethicon's procedure was in error. Ms. Wilson is an auditor, not a medical doctor. Thus, as an auditor she had no basis for her opinion. As explained above, industry standards, ISO 14971:2007 in particular, expressly do not address the ultimate judgment as to classifying risks. Nothing in Ms. Wilson's CV indicates that she has the expertise to evaluate the severity of risks that may be associated with TVT.

Comments Concerning Ms. Wilson's Discussion of "Critical Risks Ignored"

Ms. Wilson opined that Ethicon has not "addressed several known risks associated with the TVT-O device even to this day. . . . These known risks and/or failure modes include, but are not limited to: . . . degradation, . . . roping, curling, and deforming, . . . fraying and particle loss, . . . inability to remove the TVT-O device; . . . [and] stiffness." There are several errors in these opinions which I will discuss below. However, in my opinion it is important to observe first that the FDA has specifically reviewed Ethicon's complaint log and complaint trending analyses for all Gynecare products, including the TVT-O for a two year period:[120]

> Mr. Yale provided for review the firm's complaint log for all Gynecare products from 8/03 to 8/05 which is sorted by product family and control numbers (**Exhibit #31**). Mr. Yale further provided for review the complaint trend analyses for Gynecare products (**Exhibit #32**). A review of the paretos indicated that between 8/1/03 to 8/28/05, there were 584 complaints received for the TVT products, including: TVT Device/Standard single pack and three pack; TVT Abdominal Approach Kit; and TVT Obturator. The TVT top 5 complaint categories include: post-operative complications; can't attach needle to handle; urinary retention; vaginal extrusion; and mesh frayed. There were 29 cases related to post-operative complications. Of the 29 cases, there were 21 reportable events related to post-operative complications. There were 215 MDR reportable events total of which 3 were deaths, 192 were serious injuries, and 20 were malfunction related events. Ms. Brown explained that there was one death event related to the TVT Standard and one

This record shows that the FDA inspector was specifically aware of all of the complaint categories, thus including those that Ms. Wilson characterized as "critical risks ignored." Contrary to Ms. Wilson's opinions, the inspection did not result in any need for re-evaluation of

[120] ETH.MESH.02781437-ETH.MESH.02781458.

the risks associated with the complaints or re-evaluation of the overall residual risks of the TVT products.

1. Ms. Wilson's Confusion of the Terms Risk and Failure Mode

Ms. Wilson improperly interchanged the term "risk" with the term "failure mode" and avoided the necessary recognition of the term "harm." ISO 14971:2007 defines "risk":

> **2.16**
> **risk**
> combination of the probability of occurrence of harm and the severity of that harm

Thus, for Ms. Wilson to knowledgeably discuss "risks", particularly those she claims Ethicon has ignored, she should use the concepts identified in ISO 14971.

To appreciate Ms. Wilson's confusion, we need to define some other basic terms that have been used in hazard analysis and risk assessment for decades:

> **Failure Mode -** ***effect*** by which a failure is observed in a system component. [121]
>
> **Hazard -** potential source of harm.
>
> **Harm** - physical injury or damage to the health of people, or damage to property or the environment.

According to the Ethicon risk analysis procedure "Potential Failure Mode" is "a specific manner that the medical device or element of the medical device being evaluated will fail to perform one or more of its intended functions."[122] The medical device industry generally recognizes that to have an "effect" (e.g. adverse event) one must have a "failure mode". The identification of a failure mode depends on an understanding of the design requirements. Thus, failure modes would include failures to achieve design requirements such as tissue in-growth and biocompatibility.

A failure mode may or may not have an identifiable, associated harm. (For example, a failure mode may be associated with a cosmetic attribute and contribute to rejection during inspection but have no impact on implant performance or lead to a harm.) It is important to understand that by associating the term "risk" with "failure mode" instead of "harm," Ms. Wilson is attempting to gloss over a fundamental problem with her proposition of neglect: she has not identified "harm" resulting from "degradation." Thus, she has no basis for her claim that "degradation" involves "risk" as that term is defined in ISO 14971. Rather the association she has made is in direct conflict with the documentation she claims to have audited.

---

[121] IEC 812 *Standard for Analysis Techniques for System Reliability- Procedure for failure mode and effects analysis* 1985

[122] ETH.MESH.10619196-ETH.MESH.10619223.

2. Degradation

Ms. Wilson opined at length regarding degradation, but she failed to employ the proper standards associated with the analysis of risk from polymer degradation or the enormous body of knowledge that precedes her opinion to the contrary. Specifically, analysis of the potential risk from degradation of materials used in medical devices is the subject of the ISO 10993 series. These ISO standards apply to the potential risks from nearly all forms of material degradation, including chemical reactions such as oxidative degradation, and how to appraise the potential for harm. Ms. Wilson ignored ISO 10993. In fact, ISO 10993 is nowhere even mentioned in her report. A brief overview will show the importance of ISO 10993 with respect to Ms. Wilson's opinion concerning degradation.

An overriding guiding principle is now stated in ISO 10993-9:

> The level of biological tolerability of degradation products depends on their nature and concentration, and should be primarily assessed through clinical experience and focused studies. For theoretically possible, new and/or unknown degradation products, relevant testing is necessary. For well-described and clinically accepted degradation products, no further investigation may be necessary.

ISO 10993-9 further emphasizes limitations on the need for further testing as follows:

> It is neither necessary nor practical to conduct degradation studies for all medical devices. Consideration of the need for degradation studies is provided in annex A. The assessment of the need for experimental degradation studies shall include a review of the literature and/or documented clinical experience. Such a study can result in the
>
> conclusion that no further testing is needed if the product under consideration has a demonstrated history of acceptable clinical experience, new data, published data and analogies with known devices, materials and degradation products.

One of the key reasons these standards put emphasis on past clinical experience is that biodegradation studies involve the use of animals, but for ethical reasons there is an expressly stated goal to minimize the use of animals for testing.[123]

In the USA, the FDA reserves the final decision on whether degradation studies are needed by stating categorically that the appropriate division of CDRH should make the determination for additional degradation studies, not Ethicon or someone such as Ms. Wilson or myself:[124]

> **Extent of Recognition:**
>
> Complete standard with the following exceptions:
>
> Annex A - The final decision on whether degradation studies are needed should be determined by the appropriate CDRH Division.

[123] See, e.g., ISO 10993-1 at pp. 11 & 15.

[124] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=31650 (last accessed February 24, 2016).

In the case of polypropylene as an implant, by 1990 the material was already well-known, studied and characterized. In 1990 the FDA provided to Ethicon its own exhaustive biocompatibility review and research concluding that (1) any oxidative degradation of the polypropylene polymer "proceeds slowly and is generally not considered clinically significant under normal circumstances" and (2) "the cumulative risk of nonabsorbable polypropylene surgical suture breakage is small, and its ability to function properly is uncontested."[125]

Ms. Wilson's report also failed to acknowledge and consider the thorough biocompatibility risk assessments that Ethicon itself has conducted, clearly included in the materials she has cited as her reference material. In 1995 Ethicon was performing risk analyses even for its implant devices, including Prolene meshes, taking into account prior clinical experiences.[126] The analysis of Prolene mesh expressly considered biological incompatibility. At that time, analysis of the possibility of biological incompatibility was already guided by ISO 10993-1.

In 1997 in anticipation of obtaining the new CE Mark for its Prolene Mesh, Ethicon undertook efforts to demonstrate compliance with the Essential Requirements of the European Medical Directive. Ethicon documented its compliance in great detail including a risk assessment that specifically included a biocompatibility risk analysis based on detailed reports on biocompatibility testing and biocompatibility literature review as per ISO 10993 standards, and including product risk analysis and clinical history literature review as per the applicable European standard EN 1441.[127] Ethicon specifically determined that no further biocompatibility testing was needed pursuant to EN 30993, or ISO 10993.

In 2000 in connection with the development of Prolene Soft Mesh, Ethicon performed additional risk analyses that specifically again considered whether biodegradation could be a potential hazard.[128]

In 2001 Ethicon performed an additional risk analysis in connection with the TVT product and again conducted detailed literature searches.[129]

In each of these analyses, Ethicon concluded that no further degradation studies were needed for its Prolene meshes. Ethicon applied ISO 10993 by factoring into its determination the lengthy history of safe clinical use of Prolene in sutures and mesh products in a variety of applications. The FDA has repeatedly reviewed Ethicon's biocompatibility risk assessments each time Ethicon has submitted 510(k) applications for each new or modified product that has included Prolene mesh and has not requested any additional degradation studies. It is my opinion, based on my years of experience with evaluating the verification, validation and risk assessment of devices

---

125 ETH.MESH.06934664-ETH.MESH.06934688.
126 ETH.MESH.06398793-ETH.MESH.06398932.
127 ETH.MESH.16046418-ETH.MESH.16046554.
128 ETH.MESH.06399227-06399244 and ETH.MESH.06399211-06399225. These and other risk analyses were in the form of a device design Safety Assessment or DDSA as opposed to an FMEA. There is no requirement in the industry standards that the risk analysis be in one form or the other. Either can suffice.
129 ETH.MESH.10587931-ETH.MESH.10587950; ETH.MESH.00220004-ETH.MESH.00220025; ETH.MESH.00220026-ETH.MESH.00220041.

and materials for implantation in the body, the application of ISO 10993 for biomaterial qualification, and working as a liaison to numerous regulatory applications around the world, that no further degradation studies were needed for Ethicon's Prolene meshes.

Further, as a quality systems procedure auditor, it is not at all clear how Ms. Wilson is qualified to give an opinion as to whether the laboratory observations of superficial changes to the Prolene biomaterial are related to a clinical hazard, much less related to observations for mesh erosion (i.e., have the potential to do harm) – particularly given that the material had been widely used as an implantable material for decades[130] and that Ethicon had evaluated numerous peer-reviewed studies on the potential for degradation of Prolene.[131] Ms. Wilson has apparently set her opinions above those of scientists at the FDA who by 1990 supported down-classification of polypropylene sutures based on the findings that (a) its performance parameters were "well documented and understood," (b) it has a "reasonably uniform risk/benefit profile," and (c) "the polymer's degradation proceeds slowly and is generally not considered clinically significant under most circumstances of use."[132]

Ms. Wilson criticized Ethicon's IFU for the TVT device because it states that TVT is not "subject to degradation or weakening by the action of tissue enzymes." Ms. Wilson apparently lacks an understanding of how Prolene surgical mesh functions in the body as a bridge for tissue ingrowth. This is expressly stated in the portion of the IFU she cited. Studies have shown the strength of the in-grown tissue compared to the mesh properties, such that mesh strength is not the dominant support over time in the body.[133] Furthermore, the very same dog study report she cited conducted in 1992 concluded there was no significant loss in molecular weight, which is viewed as a signal of degradation.[134]

3. Fraying and Particle Loss

Ms. Wilson discussed fraying and particle loss at length and concluded "this harm to patients was not properly mitigated." Moreover, she criticized Ethicon for finding that there was "no associated harm." However, she did not identify a harm.

Ms. Wilson suggested that a presentation by Gene Kammerer demonstrates typical TVT "particle loss, fraying, degradation, roping, and deformation." However, she failed to observe that the presentation was an ad hoc demonstration of TVT mesh when subjected to intentional abuse. Ms. Wilson failed to show how these results would have any relationship to clinical outcomes. In order to place Ms. Wilson's opinions in proper context, I believe she should have considered the following finding from a physician interview:

---

130 ETH.MESH.09625731-ETH.MESH.09625736; ETH.MESH.00070044- ETH.MESH.00070045.

131 Exhibit T-2262.

132 ETH.MESH.06934664-ETH.MESH.06934688; FDA Reclassification of Nonabsorbable Polypropylene Surgical Suture.

133 ETH.MESH.00514908-ETH.MESH.00514921 (finding at page ETH.MESH00514909 that the underlying tissue is stronger than the mesh at 13 weeks in a swine study); ETH.MESH.10575784-ETH.MESH.10575805.

134 ETH.MESH.09888187-ETH.MESH.09888223.

Observations and Physician's Comments On Blue Particulate

- Physician did not comment on blue particulate until prompted.
- Physician did appear to notice particulate which fell from the tape when he cut the trocars off of the tape or when the sheaths were removed.
- After greatly stretching a leftover piece of mesh following the procedure, Physician observed that he
  a) "has not noticed as much particulate with clear mesh"
  b) 'would never stretch a tape in such a fashion during a normal procedure and that he would therefore not be concerned about mesh fragments"
- Physician suggested that he would not be concerned with the particulate during a procedure as long as he had been forewarned and was assured that the mesh properties / characteristics had not been changed and that the effect also happened with the clear mesh.

This physician interview was part of the design validation for blue TVT in 2001. This is a very clear example contradicting Ms. Wilson's opinion that Ethicon never assessed the clinical impact of particle loss.

Ethicon has properly monitored fraying and particle loss for many years now in its post market surveillance, including its complaint report files, complaint reviews, clinical expert reports and benefit-risk analyses that I have previously discussed. None of Ethicon's risk assessments or post market surveillance has indicated any need for mitigation of fraying and particle loss. Indeed, the reports of fraying or particle loss are rare in comparison to the number of devices sold and would appear to be associated with handling prior to implantation, detectable by the physician. Moreover, Ms. Wilson cited only one complaint report that suggested a frayed mesh or loose particle may have been associated with an erosion, but that complaint could not be verified. In my opinion, Ethicon has performed the requirements of Sections 5, 7 and 9 of ISO 14971:2007 with respect to analysis of the potential for a hazard associated with fraying and particle loss.

4. Roping, Curling and Deforming

Ms. Wilson's report included a section on the potential for "roping, curling and deforming" of the TVT mesh. These appear to be three terms used interchangeably as opposed to three separate attributes. Ms. Wilson opined that Ethicon never analyzed the potential for harm associated with roping, curling and deforming. Ms. Wilson is wrong. Ethicon's 2001 risk analysis expressly considered the potential for such harm due to overtensioning.[135] Overtensioning is related to roping/curling/deforming because this is what happens when the mesh is improperly stretched. This is another example of Ms. Wilson confusing the difference between cause and effect. The risk analysis stated:[136]

c) Overtensioning of tape	User	Long / critical	Failure Mode	Probable	5	-Info in IFU -Training	No	0	Acceptable
j) Prolonged urinary retention	See 28c								

In my opinion, this risk analysis properly identified the risk, its risk class and determined that the residual risk would be acceptable after mitigation in the form of IFU information and proper training.

135 ETH.MESH.10587932-ETH.MESH.10587939.
136 *Id.*

Ms. Wilson opined that Ethicon's Risk Management Report (Legacy) for TVT and TVT-O did not address curling/roping. I disagree. The report reviewed all complaints for an extended period of time. Ethicon reviewed the complaints for fraying/roping and found no associated harm was reported. Ethicon also reviewed the complaints for urinary retention and determined that the overall residual risk level for TVT was moderate. Even in those few reported instances of urinary retention, I did not find any indication that the cause was roping/curling/fraying. Ethicon's Clinical Expert Reports discussed previously confirm the validity of Ethicon's analysis in the earlier Risk Management Report (Legacy). These reports refute Ms. Wilson's opinions that Ethicon ignored roping, curling and deforming and that roping, curling and deforming were somehow "critical risks."

5. Removal of TVT-O

Ms. Wilson opined that it is difficult to remove the TVT-O device. Of course the removal of TVT is not simple. It is very clear from the design requirements that TVT-O was designed to integrate with tissue as a permanent implant. That is the purpose of the mesh.[137] Ms. Wilson criticized Ethicon for not inventing new tools for removal surgery. If surgeons wanted new tools, I would have expected Ms. Wilson to have cited complaint reports and user inputs from the surgeons requesting new tools.

I agree with Ms. Wilson that removal of any permanent implant, such as the TVT-O device, is a residual risk that cannot be eliminated. ISO 14971:2007 expressly contemplated this situation. Ethicon took the risk reduction measure to inform of the risk in the IFU following Section 6.4 of ISO 14971:2007. Moreover, Ethicon complied with Section 7 of ISO 14971:2007 by performing overall residual risk evaluation which determined that the benefits of the TVT-O device outweigh the overall residual risks. In my opinion, based upon the records I reviewed, Ethicon certainly has not ignored risks associated with the removal of TVT-O.

6. **Laser Cut TVT Mesh Complications**

While this section of Ms. Wilson's report has a heading suggesting that it deals with the subject of "stiffness," I note that the section begins with yet another discussion of particle loss. I have already addressed this subject above. However, I note that in this section she cited a Clinical Expert Report for the proposition that on average the mechanically cut mesh lost approximately twice the number of particles as the laser cut mesh. I have two observations. First, her report is in error because the Clinical Expert Report she cited had an error. The actual engineering report that studied the difference in particle loss made the following conclusion:[138]

[137] ETH.MESH.02340756-ETH.MESH.02340828, at 02340762.
[138] ETH.MESH.01219631-ETH.MESH.01219641.

> **RESULTS/DISCUSSION**
> The average particle loss following 50% elongation for mechanically cut TVT PROLENE Mesh was 0.0064% with a standard deviation of 0.0036%. The average particle loss following 50% elongation for laser cut TVT PROLENE Mesh was 0.0047% with a standard deviation of 0.0059%.
>
> ANOVA analysis was performed on the data sets and produced a p-value of 0.180 at 95% confidence, demonstrating that the two sample sets are not statistically significantly different. All statistical data analysis was performed using MINITAB Release 14, and can be seen in Appendix II. The average percent particle loss of laser cut mesh is 0.0017% less than mechanically cut mesh.

Second, I believe it is important to note again that the particle loss observed in the study was the result of intentionally abusing the TVT mesh (the mesh was stretched to 50% elongation).

Next, Ms. Wilson opined that there are problems with the elasticity and stiffness of laser cut mesh. She cited a series of emails to support a claim that the elasticity of laser cut mesh is "substantially different" from mechanically cut mesh. However, the actual email stated:[139]

> The MCM meshes stretch between, 55.8% and 33.4%. The LCM meshes stretch between, 39.5% and 32.1%. If we look at the elongation curve data and select 256 grams (2.51N) on the force axis, 1/2 the applied force of 513 due to the doubling of the mesh, we can see the curves intersect at about 7% to 10% ?? elongation. The scale is off a bit due to transposing of the graph into the e-mail.
>
> So, we are close to the range we have identified as important, and the LCM mesh is very similar to the MCM mesh and in fact falls with in the boundries of the small data set for the MCM. This elasticity test, which was set up by Medscan and Dr. Ulmsten is the only elongation characteristic by which the acceptability of the mesh was measured, and the LCM passes as well as falls within the range of the MCM.

Thus, we see that in fact the elasticity of the two meshes were "very similar," not "substantially different."

Ms. Wilson then cited another Ethicon memo to support her statement that laser cut mesh is three times stiffer than mechanically cut mesh. Again, she omitted the key findings:[140]

> **Results**
> The average load at ¼" intervals of elongation, up to 1" (20%) of elongation was calculated for both groups of TVT mesh and is plotted below in the Figure along with several meshes from competitor devices. At 1" of stretch, the laser-cut TVT mesh was about three times stiffer than than the machine-cut TVT mesh, however the laser-cut TVT mesh was still less stiff and was exhibiting lower resistance load than all competitor meshes.

[139] ETH.MESH.00302181-ETH.MESH.00302184.
[140] ETH.MESH.01809080-ETH.MESH.01809081; see also ETH.MESH.06696357-ETH.MESH.06696361.

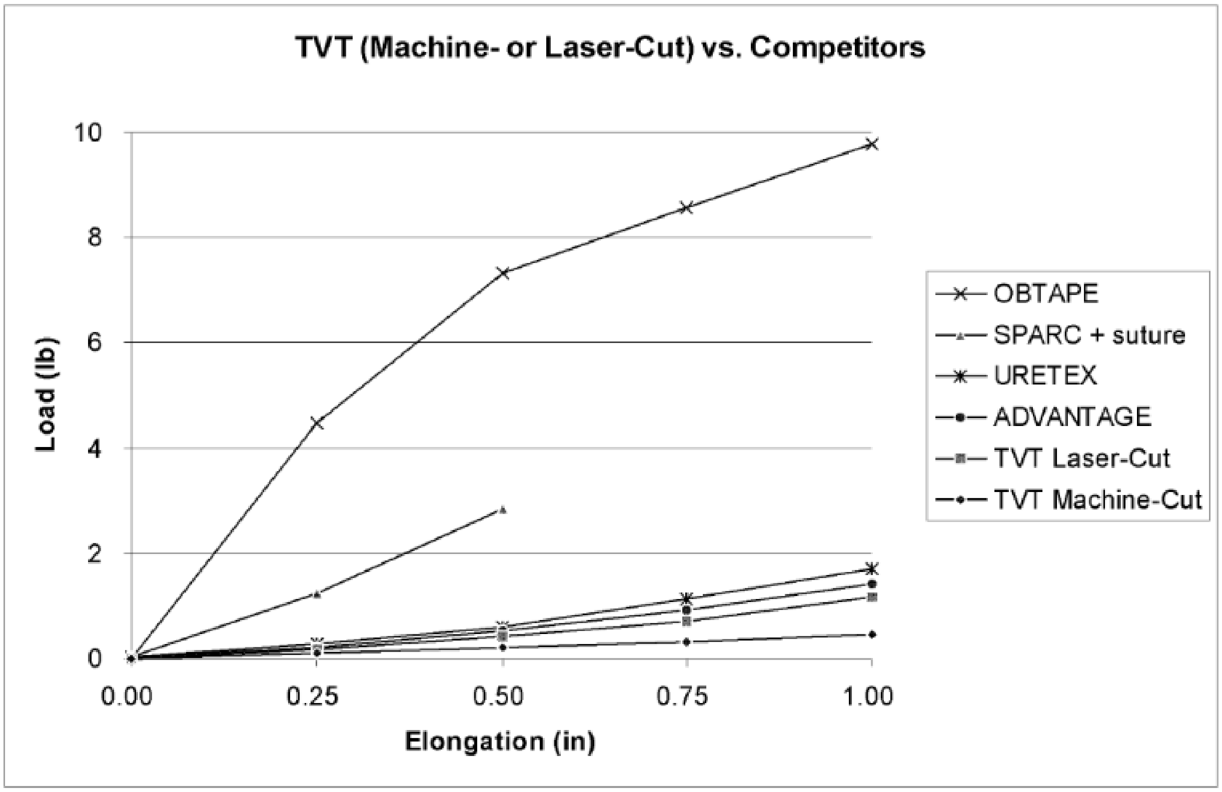

Figure: Tensile Behavior of TVT and Competitor Meshes

Ms. Wilson ignored the fact that the stiffness of laser cut mesh was less than all of the competitor products analyzed and was thus well within the range of acceptability. Again, the facts show that the differences between laser cut and mechanical cut mesh did not introduce a new risk when compared to existing marketed products.

Ms. Wilson opined that it was not within the "industry norms" for Ethicon to rely on the performance of other products to conclude that "stiffness" did not introduce a new risk for its laser cut mesh. I disagree. In fact, ISO 14971:2007 and ISO 10993 expect the manufacturer to review and apply, where appropriate, the existing knowledge of similarly marketed devices. Moreover, both the FDA premarket notification and Medical Directive actually require medical device manufacturers to conduct and document the type of comparisons that Ms. Wilson criticized Ethicon for performing.[141] Ms. Wilson's opinion that Ethicon "should have" conducted clinical testing is without basis in light of these standards, industry norms and U.S. federal regulations.

Ms. Wilson cited Ethicon documents and literature for the proposition that complications can arise if a mesh is too stiff. However, Ms. Wilson then leapt to the conclusion that Ethicon's laser cut mesh is too stiff without offering any explanation other than to mis-attribute results from test reports about physical properties.

141 See, e.g., http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080235.htm (last accessed February 28, 2016).

Ms. Wilson's opinion that Ethicon failed to warn of the potential for "Pain, Damage to Urethra, Urethral Impingement, Damage to Bladder" is also wrong.[142]

In summary, Ms. Wilson has failed to support her opinion that stiffness is a critical risk for laser cut mesh and her opinion that Ethicon's assessment of the material was "not consistent with industry norms."

Comments Concerning Ms. Wilson's Discussion of Warnings

One of the most blatant misrepresentations of facts is the way the Ms. Wilson distorts the testimony of Dr. Meng Chen, Ethicon's Medical Director and Safety Surveillance Director. In Ms. Wilson's report she puts in quotations that Dr. Chen "repeatedly observed" complaints of "dyspareunia" and that management disregarded her.[143]. But a review of Dr. Chen's testimony reveals the flaws in Ms. Wilson's critique. Ultimately, to the contrary, Dr. Chen's testimony demonstrates she was clearly doing what she was supposed to do, but which Ms. Wilson says Ethicon did not do. In her capacity as a director (executive management) Dr. Chen was monitoring and feeding back into the system for continuous improvement of communication to patients.

Ms. Wilson also claims Ethicon management never addressed these issues raised by Dr. Chen with corrective action. She alleges that "*Ethicon management's inaction on this issue, as required by the foregoing design standards, fundamentally ignored patient concerns and the safety of this permanently implantable device.*" But again Ms. Wilson grossly distorts the facts.

- Firstly, standards for the design process are not the standards which address the assessment of post-market surveillance and customer communication after the product is released.
- Secondly, any changes to labeling after product release requires many layers of professional review, which is exactly what is taking place as described in Dr. Chen's testimony, but her testimony is misrepresented.
- Ms. Wilson distorts Dr. Chen's testimony and email to appear that Dr. Chen was raising issues and management was ignoring her. In reality, the patient brochure was updated as a result of Ethicon's monitoring of these complaints.
- Importantly, although Ethicon can at any time propose changes to device labeling, once a product is cleared, it requires a decision process to determine if a new 510(k) is required; or for regulatory authorities from other countries who may also need to agree in advance.
- Last, but not least, Dr. Chen ***is management***!

As an auditor I suppose Ms. Wilson might not appreciate that once FDA posted its notice in 2008 titled, "*FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence*", a medical device manufacturer would have certainly consulted with the FDA

[142] See Ethicon's IFUs, e.g., ETH.MESH.02340756-ETH.MESH.02340828.
[143] Deposition of Meng Chen, October 29, 2013, 121:13-19.

prior to changing any labeling.[144] The suggestion made by Dr. Chen to consider a coordinated update to any changes to device labeling was prudent considering the complexity of labeling changes. Unlike what Ms. Wilson naively implies, Ethicon management would have been irresponsible had they made labeling changes solely on the basis of Dr. Chen's email, and without consultation with FDA and clinical experts in the field over wording, content and recommended actions. None of the documents that Ms. Wilson stated she reviewed supports her contention that Dr. Chen was ignored. In my opinion, this is a misrepresentation of facts.

FACTS OR DATA CONSIDERED IN OPINION

The facts and data that I have considered in arriving at my opinions are referenced above throughout my report. Additional materials that I have considered are also listed in Exhibit A.

EXHIBITS

I have not yet determined what exhibits I may use at trial to explain my opinions. I will do so in accordance with the instructions I receive from the court and counsel.

COMPENSATION

The rates at which I am being compensated are as follows:

- $250 per hour for time spent not involving travel;
- $325 per hour for time spent including travel, deposition, or trial testimony.

CASES IN WHICH TESTIMONY HAS BEEN GIVEN

Deposition taken October 6, 2015 in *In Re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation*, Master File 2:12-MD-MDL 2327 in the United States District Court for the Southern District of West Virginia, Charleston Division.

---

144 http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm (last accessed February 28, 2016).

RESERVATION OF RIGHTS AND SIGNATURE

The fact that I do not explicitly mention all Ms. Wilson's statements should not be understood as an agreement with her statements. Moreover, my opinions are expressed to a reasonable degree of professional certainty within my field of expertise. I have reviewed voluminous documents but reserve my right to evaluate additional documents in the future and revise or supplement my opinions as necessary thereafter.

Elaine Duncan

Digitally signed by Elaine Duncan
DN: cn=Elaine Duncan, o=Paladin Medical, Inc., ou=President, email=duncan@paladinmedical.com, c=US
Date: 2016.03.01 10:23:38 -06'00'

Elaine Duncan, M.S., M.E., RAC
President of Paladin Medical, Inc.
Date: February 29, 2016